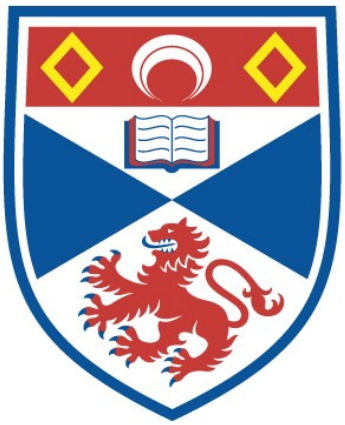
THE REACTIVITY OF SOME ORGANOPHOSPHORUS ESTERS

David Thomas Eastlick

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1969

THE REACTIVITY OF SOME ORGANOPHOSPHORUS ESTERS

A Thesis
presented for the degree of
Doctor of Philosophy
in the Faculty of Science of
the University of St. Andrews

by

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United College of St. Salvator
and St. Leonard,
St. Andrews.

September, 1969.

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TO MY WIFE

DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes results of research carried out in the Department of Chemistry, United College of St. Salvator and St. Leonard, University of St. Andrews, under the supervision of Professor J.I.G. Cadogan since 1st October, 1966, the date of my admission as a research student.

CERTIFICATE

I hereby certify that David Thomas Eastlick has spent twelve terms at research work under my supervision, has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

Director of Research.

GENERAL LIST OF CONTENTS

ACKNOWLEDGEMENTS

I should like to express my thanks to Professor J.I.G. Cadogan for suggesting the topics of research, and gratefully acknowledge my indebtedness to him for his constant interest, advice, and encouragement throughout the three years during which the work was carried out.

I am also appreciative of the helpful suggestions and assistance from many members of the teaching and technical staff of the Chemistry Department in the University of St. Andrews.

The Science Research Council is also to be thanked for the award of a Research Studentship during the period of this work.

SYMBOLS AND ABBREVIATIONS

The abbreviations that appear in this thesis are those in common usage. In addition, the following symbols are used:

J	spin - spin coupling constant.
R_f	ratio of the distance moved by the substance to the distance moved by the solvent front.

Infrared absorption frequencies are described as stretching (ν) or deformation modes (δ) and the relative intensities described as strong (s), medium (m) or weak (w).

In keeping with general usage, the term phosphyl is taken to embrace phosphonyl, phosphoryl, phosphinyl, and phosphine oxides.

P A R T I :

THE REACTION OF o-DINITROBENZENE WITH TERVALENT PHOSPHORUS COMPOUNDS

ABSTRACT OF PART I

The occurrence of bimolecular nucleophilic aromatic substitution has been established in the reaction of o-dinitrobenzene with triethyl phosphite and diethyl methylphosphonite in acetonitrile solution. There is a fine balance between the customary deoxygenation and nucleophilic substitution of aromatic nitrocompounds. The role of the o-nitro group in facilitating the nucleophilic substitution has been discussed in terms of "built-in solvation" of the reaction centres.

The exclusive formation of ethyl nitrite in the reactions has been shown to be compatible with the dealkylation of a quasi-phosphonium intermediate by nitrite ions.

CONTENTS OF PART I

INTRODUCTION

Preamble

As a continuation of their studies of the reactions of alkyl phosphites with aromatic nitro-compounds, Cadogan and his co-workers found a simple, one-stage reaction to yield diethyl o-nitrophenylphosphonate from o-dinitrobenzene and triethyl phosphite.[1a] The reaction was unique in two respects: none of the usual deoxygenation products of nitro-compounds were observed[2] but direct displacement of a nitro group occurred to give o-nitrophenylphosphonates. Before this route was discovered, the methods of synthesis of these compounds either failed or gave low yields of products separable only with difficulty.

Previous Methods of Synthesis of Dialkyl o-Nitrophenylphosphonates

Of the established methods of synthesis,[3] the method involving phosphorus trichloride and o-nitrobenzene diazonium fluoroborate in the presence of copper in anhydrous media fails to give product.[4] The direct nitration of phenylphosphonic acid is complicated by the isomeric mixtures obtained. The phosphonyl

group is not exclusively m-directing, although this isomer predominates. o-Nitrophenylphosphonic acid was retained in the solution from the nitration mixture, while the m-isomer was precipitated as its magnesium salt.[5]

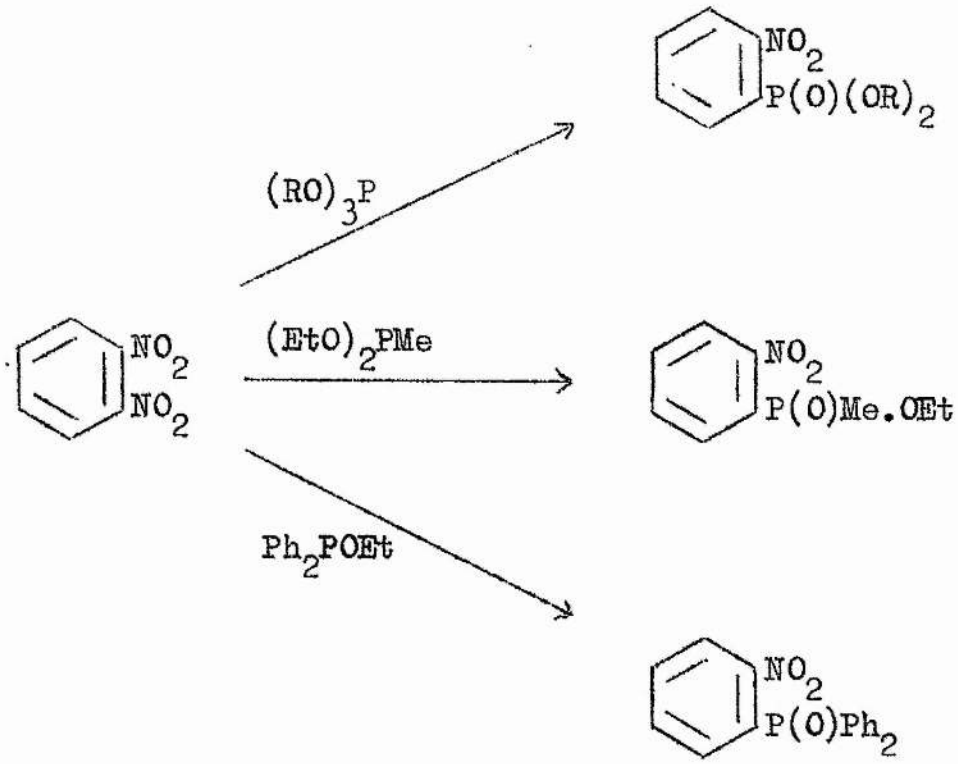
Griffin and Obrycki also reported failure to form o-nitrophenylphosphonic esters by their free radical modification of the Michaelis-Arbusov reaction, using trialkyl phosphites as radical traps for aryl radicals generated by photo-initiation from aryl iodides.[6a,6b] In contrast to their many successful preparations, o-nitroiodobenzene yielded tars and the corresponding trialkyl phosphate. This parallels the thermal deoxygenations of nitro groups to form an electron-deficient species (nitrene), a subject recently reviewed by Cadogan.[2]

The failure of these methods of synthesis highlights the high yields (75%) obtained by Cadogan, Sears, and Smith[1] of diethyl o-nitrophenylphosphonate by reaction of triethyl phosphite with o-dinitrobenzene.

Further Background to the Reaction of o-Dinitrobenzene with Phosphorus Nucleophiles

The reaction was extended to other tervalent phosphorus compounds: ethyl diphenylphosphinite, diethyl methylphosphonite, triisopropyl and trimethyl phosphites to yield analogous

products[1b] (Scheme 1).



Scheme 1

The products were obtained in high yield with little or no evidence of the usual deoxygenation of nitro groups by tervalent phosphorus compounds. The relative reactivity of these compounds, $EtOPPh_2$ > $(EtO)_2PMe$ > $(RO)_3P$, parallels the order of decreasing nucleophilicity. Trialkyl phosphites required boiling in acetonitrile (8 hours, 80°) to give the product in 80% yield. Diethyl methylphosphonite required more moderate conditions (20 hours, 18°) to yield the phosphinate product (77%), whereas ethyl

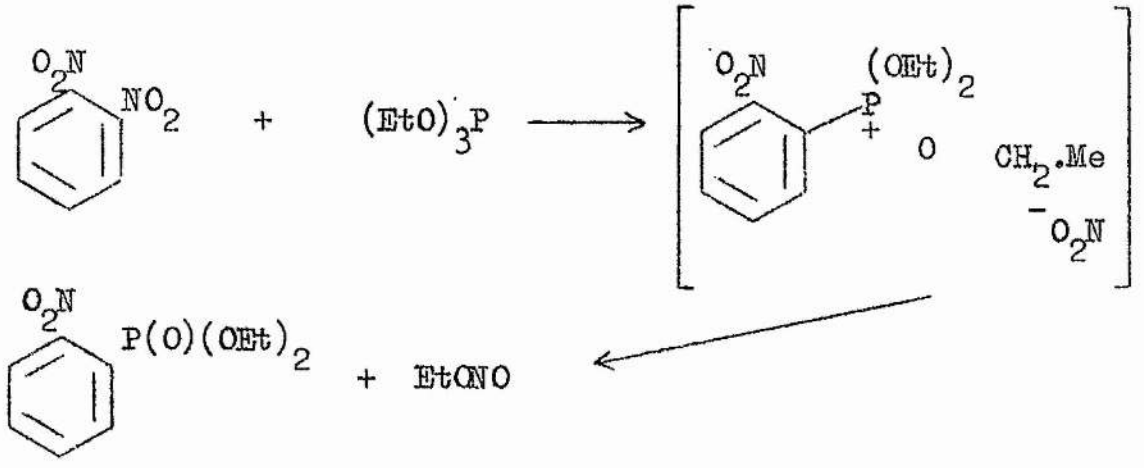
diphenylphosphonite required the addition of reagents at -10° before being kept at 18° for 12 hours to yield the corresponding phosphine oxide (65%).

Other substrates investigated by Cadogan, Sears, and Smith were 1-nitro-2,4-dinitrobenzene, which was converted into dimethyl 2,4-dinitrophenylphosphonate (73%) and 2-nitropyridine-1-oxide which yielded diethyl 2-pyridylphosphonate (35%). The chlorine ator in 1-chloro-2,4-dinitrobenzene was less easily displaced by triethyl phosphite to yield diethyl 2,4-dinitrophenylphosphonate (11%) as was the p-tolylsulphinate group from 4-methyl-2'-nitrodiphenylsulphone to give diethyl o-nitrophenylphosphonate (8%).

One reaction, that of o-dinitrobenzene and triethyl phosphite, was shown not to be photocatalysed for formation of the substitution product.

The more reactive phosphines gave tars with the nitrocompounds used so far. Under no circumstances did m- or p-dinitrobenzenes yield substituted phosphonates. Deoxygenation was observed to be the pathway in these cases, to yield tars. Other substrates that were investigated were 2-nitropyridine, 4-nitropyridine-1-oxide, o-chloronitrobenzene, and o-nitrobenzenediazonium fluoroborate with triethyl phosphite. Without exception, these compounds yielded no substitution products.

The suggested mechanism for this reaction [1b] by Cadogan and his co-workers was a nucleophilic aromatic substitution followed by dealkylation by nitrite ion of the phosphonium intermediate Scheme 2).



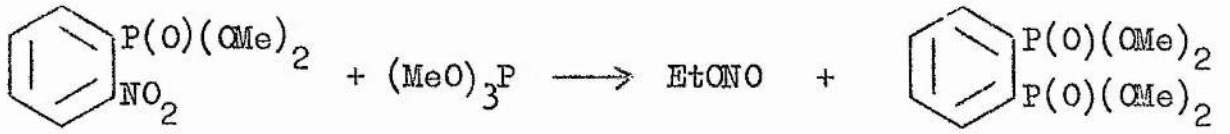
Scheme 2

Such a scheme, however, does not fit all of the experimental observations.[1b] Points which tell against the scheme are:-

(i) p-Dinitrobenzene was shown not to undergo a similar substitution of one of its nitro groups. No detectable phosphonate formation occurred, but only deoxygenation to yield tarry residues. No substitution was observed with o-chloronitrobenzene, which, like p-dinitrobenzene, has been used as a substrate for nucleophilic substitutions.[8] A small quantity of substitution product (8%) was however obtained from 4-methyl-2'-nitrodiphenylsulphone and triethyl phosphite.

(ii) No nitroethane was formed by the attack of the ambident nitrite ion on the phosphonium intermediate.

(iii) The diethyl phosphonyl group has the same order of deactivation as a nitro group,[9] and it would have been expected that substitution would have occurred to yield a phenylene bisphosphonate (Scheme 3).



Scheme 3

Such formation would parallel the photo-initiated arylation of trialkyl phosphites, where with o-dihalogen substituents, phenylene bisphosphonates are formed. The lack of reaction was attributed to the large blocking effect of the phosphonyl grouping, although this has to be compared with Griffin and Obrycki's reaction[6b] where displacement of the second halogen is accelerated, giving rise to displacement even in the case of chlorine. However, in the photoreaction a radical species is formed, which has less stringent steric requirements than a substitution at the aromatic ring.

At this point, where the known facts of the nitro displacement from o-dinitrobenzene and related compounds with tervalent

phosphorus nucleophiles have been reviewed, it is opportune to examine nucleophilic aromatic substitution as a vehicle for describing the reaction.

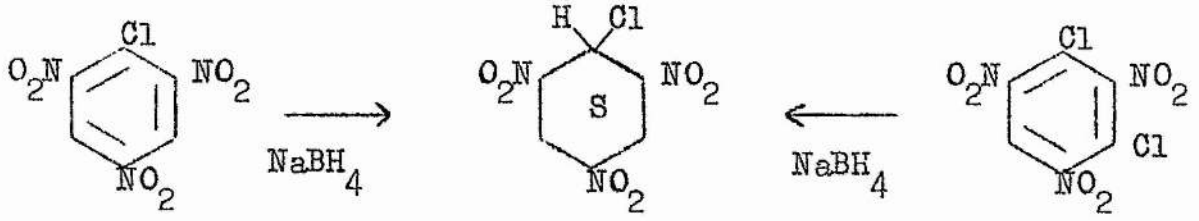
Nucleophilic Aromatic Substitution

In nucleophilic aromatic substitution, the attacking species is an electron donor, so the reaction is facilitated in the first instance by the presence of electron withdrawing substituents in the aromatic ring. The most common activating group is nitro, although similar activation can also be provided in heterocyclic molecules, particularly if the heteroatom (nitrogen) is quaternised or exists as a 1-oxide.[10]

Nitro groups activate an aromatic ring by an electron attracting action made up of two parts - an inductive and a mesomeric component. The inductive (-I) component will be greatest at the ortho position, while the mesomeric contribution will act over the whole aromatic ring. The mesomeric component is strongly suppressed when coplanarity of the nitro group with the ring is prevented by bulky neighbouring substituents.[11]

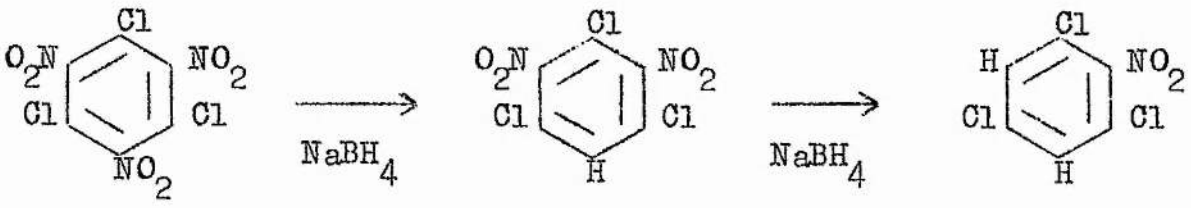
The effect of steric hindrance on the mesomeric withdrawal of electrons by nitro groups has been well demonstrated by Kaplan.[12] The products of hydride additions to the chloro- and dichlorotri-

nitrobenzenes (1) and (2) are sufficiently long-lived to allow further additions leading to the non-aromatic cyclohexane product (3). Crystallographic evidence shows that the nitro group is no more than 30° out of the plane of the benzene ring, thus allowing mesomeric interaction.



(1) (3) (2)

In trichlorotrinitrobenzene (4) a nitro group is displaced. Crystallographic results show that the O-N-O plane of the group is at 76° to the benzene ring, i.e. there is zero or minimally zero resonance. A nitro group is now displaced in accordance with the known mobilities[8,13] of nitro and chlorine substituents.



(4)

The leaving group is generally a stable anion and nitro is second only to fluorine in its exceptional mobility as a leaving group.[8,13] The rate of substitution of the halogenonitrobenzenes

generally decreases in the order halogen I < Br < Cl ≪ F.[8,13,14] Thus, the acceptance of a negative charge by the carbon to which the halogen is attached, which facilitates the addition of the base to the ring, has a stronger effect on the reaction rate than the leaving tendency of the halide ion. A reversal of this order has been found on occasions.[14]

Photochemical substitutions of the nitro group have been observed in trinitroaromatics,[15] p-nitrophenylphosphate and p-nitroanisole.[16] In the latter work Ramsey et al. found that pyridine in dilute aqueous solution gave 1-aryl pyridinium nitrites when the reaction was irradiated with light with wavelength >289nm. Johnson and Rees[17] reported that light accelerates the formation of 4-piperidinopyridine-1-oxide from 4-nitropyridine-1-oxide and piperidine. Both the photochemical and dark reactions afforded the same product.

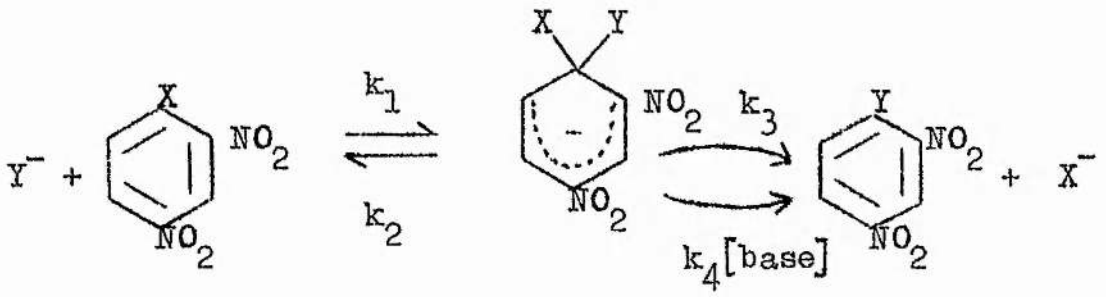
Bimolecular Nucleophilic Displacement

There are three general mechanisms of nucleophilic substitution: (a) unimolecular, exemplified most clearly by the decomposition of diazonium salts, (b) one involving a benzyne intermediate and cine substitution, and (c) a bimolecular process.[14] Since later in this work it will be shown that the bimolecular mechanism operates in the o-dinitrobenzene/phosphite

system, the benzyne and unimolecular mechanisms will not be further discussed.

The general character[18] of a bimolecular nucleophilic aromatic substitution is generally agreed to be the reversible formation of a tetrahedral intermediate, decomposition to products occurring either spontaneously (k_3) or in a base-catalysed step (k_4, where this is applicable, for instance with amine substitution) (Scheme 4).

It is generally assumed that less activated aromatic substrates react in the same way, although there is little direct evidence for this. The tetrahedral intermediate loses aromaticity as a result of partial bond formation with the nucleophile; the

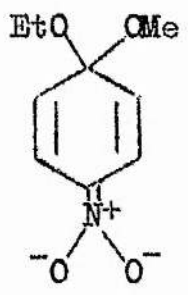


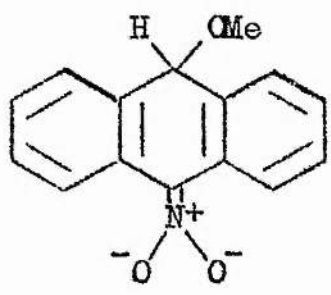
Scheme 4

carbon atom at the reaction centre now assumes sp^3 hybridisation. Some resonance stabilisation of the intermediate is possible, and this will be facilitated by the presence of nitro groups. There are two limiting conditions (Scheme 4). If k_3 or k_4[base] is

greater than k_2, then the rate-determining step is the formation of the intermediate. If on the other hand k_2 is greater than k_3 or k_4[base], then this is a measure of the rate of bond rupture in the substrate.

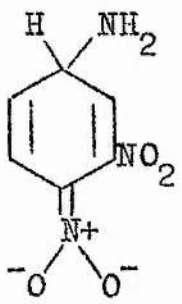
The evidence for such a two-step mechanism is quite complete. The tetrahedral intermediate formed is analogous to the complexes first discovered by Meisenheimer.[19] These were obtained by mixing alkoxides with polynitro-compounds and Meisenheimer found that he obtained the same salt (5) either by treating s-trinitroanisole with potassium ethoxide or s-trinitrophenetole with potassium methoxide. The product of either route was decomposed by acid to give the same mixture of anisole and phenetole. Similar adducts (6) with potassium methoxide and 9-nitroanthracene were also obtained.[19]

(5) 

(6) 

The formation of addition compounds has been invoked by Ross in his review[14] to explain the conductance of m-dinitrobenzene in liquid ammonia to be that of a typical salt. He suggested that

an ammonium ion and an anion (7) are formed. A similar explanation of the cryoscopically determined i factor of greater than unity for some aromatic polynitro-compounds dissolved in ethanolamine was suggested[14] to be due to the formation of an ethanolammonium ion and an anion (8).



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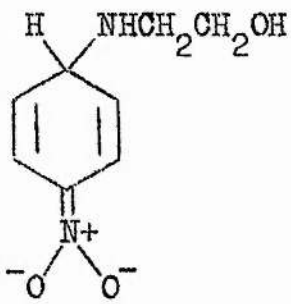

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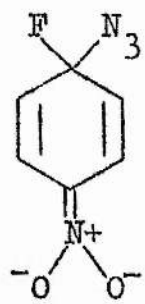


(9)

Evidence for the existence of a tetrahedral intermediate comes from the observations of Bolton et al.[20] p-Nitrofluorobenzene in dry dimethylformamide took up sodium azide in a second order process. As azide ion was consumed, an absorption at 397 nm. resembling that of a p-quinoid structure grew in intensity. No fluoride ion was released. On the addition of water the absorption at 397 nm. disappeared with the formation of p-azidonitrobenzene. These observations are consistent with the existence of an intermediate (9).

The most convincing evidence for a two-step mechanism is that of observed general base catalysis in the attack of amines on

aromatic substrates, either by the amine itself or by some added base.[21a] The reaction[21b] of butylamine and 2,4-dinitrochlorobenzene (DNCB) in water-dioxan mixtures was shown to follow the complex rate equation (a):-

$$\text{Rate} = k_n[BuNH_2][DNCB] + k_{gb}[BuNH_2]^2[DNCB] + k_{\bar{O}H}[BuNH_2][DNCB][\bar{O}H] \quad (a)$$

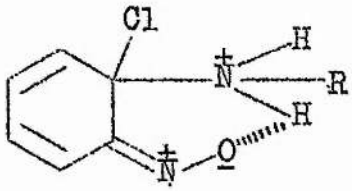
Both the second and third terms indicate general base catalysis, in the second by another molecule of amine and in the third by a hydroxide ion. Under the experimental conditions used, termolecular collisions were of low probability and the observance of third-order terms was indicative of a combination between the amine and aryl hydride initially to form an intermediate that had sufficient half life to be attacked by a second molecule of base to give products.

The two-step process has been used to explain the similarity of reaction rates of piperidine with six different 1-substituted 2,4-dinitrobenzenes in methanol at 0° to form 2,4-dinitrophenylpiperidine.[22] The rates differ by less than a factor of five for substituents in the order of decreasing rate $-SOPh$, $-Br$, $-Cl$, $-SO_2Ph$, $-OC_6H_4NO_2$, $-I$. The rates with $-F$, $-NO_2$, and $-OSO_2C_6H_4.Me-\underline{p}$ were appreciably faster. The small factor encompassing the rates was in accord with a tetrahedral intermediate, the formation of which was rate-determining.

Ortho:para Ratio of Substitution Products

The ortho:para ratio is relevant to the discussion of o-dinitrobenzene and tervalent phosphorus nucleophiles. The variation of the ortho:para ratio in rate constants, k_o/k_p, with ortho and para disubstituted benzenes has been well established.[14] Substitutions involving amines react more quickly with o-nitro-substituted benzenes than with p-nitrosubstituted benzenes, but in substitutions not involving the removal of a proton at any stage, as with alkoxides, it is the p-nitrosubstituted compound which reacts more rapidly. The ratio k_o/k_p is also solvent dependent, being highest in aprotic solvents.

To explain the more rapid reaction of amines with o-nitro-substituted compounds, Chapman[23] et al. proposed hydrogen bond formation in the transition state (10). This would not be possible



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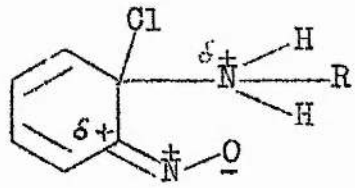


(11)

for p-substituted compounds. With hydrogen bonding some loss of mesomeric stabilisation occurs as the nitro group is no longer

coplanar with the aromatic ring. Bunnett and Morath[24] have suggested the interaction of positive and negative poles in the transition state (11) for the case of o-nitrosubstituted benzenes. This provides its own "built-in solvation", thus decreasing the need for participation of solvent molecules. They did note that their experiments could not allow them to decide whether the interaction was direct electrostatic interaction, or a matter of hydrogen bonding.

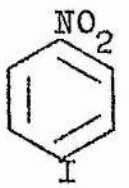
Ross[14] has provided evidence which points towards the acceptance of the Chapman hydrogen bonding hypothesis. He has reported in his review[14] the value of the ratio k_o/k_p with a tertiary amine and o-nitrochlorobenzene, where in the transition state there is no possibility of hydrogen bond formation, but only direct electrostatic interaction between neighbouring positive nitrogen and negative oxygen atoms. In benzyl alcohol at 150°, k_o/k_p for the reaction of triethylene diamine and o- and p-nitrochlorobenzenes was less than 0.004. Under the same reaction conditions with dibutylamine, a secondary amine, where hydrogen bonding can now occur, k_o/k_p was greater than 16.

Steric Effects

Nucleophilic aromatic substitutions are not generally greatly susceptible to steric influences of the bulk of large groups ortho

to the site of substitution.

A study by Sandin and Liskear[25] demonstrated some deactivation by o-halogen substituents which, for their electronic influence alone, would be activating.



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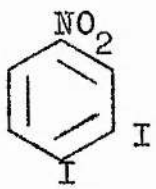

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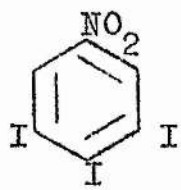
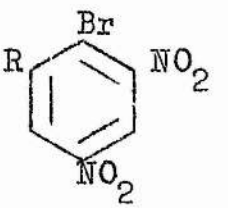


(14)

The introduction of an iodo atom into the 2-position (13) of 1-iodo-4-nitrobenzene (12) caused an approximate five-fold increase in its reactivity, due to the inductive (-I) effect, towards piperidine in boiling benzene. The substitution of a second iodine atom into the 6-position (14) caused a six-fold decrease in reactivity. If the same degree of reactivity was carried over to 3,4,5-triiodo-1-nitrobenzene (14) by the inductive effect of the second iodine atom, then the decreased rate of reaction is due to the bulk of the substituents.

Greater steric interaction has been demonstrated by Fierens et al.[26] in their rate determinations of iodide ion substitution with 6-alkyl-1-bromo-2,4-dinitrobenzenes (15). Their results showed that with the set of substituted compounds (15) with

R = Me, Et, Pr^i, and Bu^t, a strong decelerating steric effect was only shown by the t-butyl substituted compound.



(15)

Steric hindrance of the attacking nucleophile has also been demonstrated for bulky reactants by a neighbouring methyl group.[11] A diminution of rate was caused by the substitution of a methyl group into the 6-position of 1-chloro-2,4-dinitrobenzene in the reaction with methoxide ion, aniline, and piperidine. The reductions in rate were $^1/_{14}$, $^1/_{22}$, and $^1/_{276}$ respectively. It would be expected that a slight decrease in rate would result from the inductive effect (+I) of the methyl group and this is seen with aniline and methoxide ion. With piperidine a very much larger reduction occurs, resulting from effective steric inhibition.

Brady and Cropper[27] reported that the reaction of a number of alkylamines and dialkylamines with 1-chloro-2,4-dinitrobenzene gave rate constants which were not directly related to their basic strength. For instance, dimethylamine had a rate coefficient 30,000 times that of diisopropylamine, in spite of the latter being

a stronger base. These authors correlated their work with strong steric effects resulting from front-side interference by alkyl groups branching from the nitrogen atom or the adjacent carbon atoms.

Evidence for the lack of steric interaction with neighbouring nitro group comes from the investigations of Pietra and Del Cima[28] of piperidine, 2-methylpiperidine, and trans 2,6-dimethylpiperidine with o- and p-nitrofluorobenzenes and 2,4-dinitrofluorobenzene. They obtained similar amine rate ratios with each substrate and an almost constant ortho:para activation ratio upon changing the nucleophile. They interpreted these results as pointing to evidence of a tetrahedral transition state in which steric inhibition of resonance of o-nitro group was not pronounced. In such a transition state, repulsive interaction involving the o-nitro group and the leaving group could be minimised by the former inserting itself between the entering and leaving groups, coplanarity or near coplanarity being thus obtained with the benzene ring. The large drop in rate caused by the introduction of a 2- or 6-methyl group into the piperidine reagent was due to steric compression of the amine molecule against the benzene carbon and hydrogens in the transition state.

Nucleophilic Aromatic Substitutions of o-Dinitrobenzene

Substitutions have been reported by Laubenheimer[29] and

Steger.[30] The latter was a kinetic investigation with alkoxide/alcohol nucleophile and yielded a k_o/k_p ratio of 0.11 at 35° for o- and p-dinitrobenzenes. Laubenheimer found that alcoholic ammonia at 110-120° quickly converted o-dinitrobenzene into o-nitroaniline, but the p-dinitrobenzene required temperatures above 150° to substitute either an amino group or an alkoxyl group from the solvent.

Programme of Research

Cadogan, Sears, and Smith have extended the original reaction of o-dinitrobenzene and triethyl phosphite to include (a) other substrates which are capable of undergoing nucleophilic aromatic substitution, and (b) other phosphorus nucleophiles. A mechanism involving nucleophilic aromatic substitution was proposed for these reactions, but there are three pieces of experimental evidence which do not fit simply into the proposed reaction scheme.

The failure of o-chloronitrobenzene and p-dinitrobenzene to act as substrates points against such a scheme as does the lack of further substitution of the dialkyl o-nitrophenylphosphonate product, where the dialkyl phosphonyl group is as deactivating towards electrophilic attack[9] on the aromatic ring as is a nitro group.

Since the nitrite ion is ambident in nature, the lack of

formation of nitroethane in the dealkylation of the proposed quasi-phosphonium intermediate was unexpected.

The aim of the present work was to establish the generality of the o-dinitrobenzene/tervalent phosphorus reagent reaction as an aromatic nucleophilic substitution by a kinetic study. A more detailed investigation of the stability of the products ethyl nitrite and dialkyl o-nitrophenylphosphonate to the tervalent phosphorus compound was also necessary. The exclusive formation of ethyl nitrite had to be examined more closely by studying the dealkylation of a quasi-phosphonium nitrite prepared *in situ*.

EXPERIMENTAL

Infrared Spectroscopy

Liquid samples were examined as thin films, solids as nujol mulls. Spectra were usually recorded on a Perkin-Elmer Model 257 spectrophotometer.

Ultraviolet Spectroscopy

A matched pair of 1 cm. silica cells was used in Unicam S.P.800 (qualitative work) and Unicam S.P.500 Series 2 (quantitative work) spectrophotometers.

Solvents

Acetonitrile (b.p. 80-81°), benzonitrile (b.p. 66°/18 mm.), and methylene chloride (b.p. 44°) were dried by refluxing over phosphorus pentoxide and stored over molecular sieve. Diethyl ether ('ether') was dried by refluxing over calcium hydride and the distillate stored over sodium. Dimethylformamide was dried by standing over calcium hydride for three days, followed by filtration and distillation.

Reagents

o-Dinitrobenzene was crystallised twice from ethanol to give

pale yellow needles, m.p. 116-116.5°. Fluorene was crystallised from the same solvent to give white needles, m.p. 114°. Dibutyl (b.p. 135-136°/0.09 mm.) and dimethyl (b.p. 90°/0.05 mm.) phthalates were dried over drierite and fractionated to give g.l.c. pure fractions.

Triethyl (b.p. 59-61°/23 mm.), trimethyl (b.p. 53°/73 mm.) and triisopropyl (b.p. 63-64°/11 mm.) phosphites were dried over sodium wire and fractionated under nitrogen. Diethyl methylphosphonite was supplied by C.D.E.E. Porton Down, and was used without further purification.

Nitroethane (b.p. 114°) was dried over magnesium sulphate and fractionated twice to give a g.l.c. pure fraction. Amyl nitrite was prepared by the method of Vogel [31a] and a sample donated by Dr. J.T. Sharp. A sample of ethyl nitrite was donated by Dr. M.J.P. Harger.

Diethyl ethylphosphonate (b.p. 76-80°/18 mm.) was prepared by the Arbusov reaction between ethyl iodide and triethyl phosphite. Kornblum's method [32] was used to prepare silver nitrite and the yellow product was dried under high vacuum over sodium hydroxide pellets until the infrared spectrum showed an absence of hydroxyl stretching frequencies.

Measurement of Rates

Rates were measured in acetonitrile solvent in sealed pyrex tubes. The tubes were soaked in chromic acid, washed thoroughly and dried at 110° for several days before use. Solutions of known concentrations of o-dinitrobenzene, phosphorus compound and internal marker (see below) were made up and 1 ml. of each pipetted into a test-tube. This was immediately cooled in a card-ice acetone bath, while being flushed out with nitrogen, and sealed. The tubes were kept in dry-ice until required for use. They were incubated in a constant temperature oil bath (± 0.05°) for runs 40-90° and in a water bath (± 0.01°) for runs less than 40°. At known intervals of time, the tubes were quenched in dry-ice slush and analysed by gas-liquid chromatography.

A Griffin and George D.6 chromatograph was employed with 2 m. x 5 mm. i.d. packed columns and oxygen-free nitrogen as the carrier gas. The column packing was 2% neopentyl glycol succinate on 80-100 mesh Chromsorb W (abbreviated to 2% NPGS) operated at 176° with a flow rate of 50-60 ml./min.

The mole % of each component was calculated from the area of the peak since the D.6 chromatograph employs a gas-density balance detector. The area of the peak is related to the number of moles of compound injected as follows (equation b):-

$$n = \frac{kA}{M-m} \qquad (b)$$

n = no. of moles injected

m = molecular weight of carrier gas

A = area of peak

M = molecular weight of compound

k = a constant dependent of the characteristics of the chromatograph.

If an unreactive internal marker is weighted into the reaction mixture, then there exists the relation from (b) of (c):-

$$\frac{N_p}{N_s} = \frac{A_p}{A_s} \frac{(M_s - m)}{(M_p - m)} \qquad (c)$$

where subscript 's' and 'p' denote internal marker and product respectively. Areas were calculated by the "half width method". The area is equal to the product of the maximum height and the width at half this height measured from the outer edge of one side of the peak to the inner edge of the other.

A number of different internal markers were used depending on the circumstances. Initially dibutyl phthalate was used for following the formation of diethyl o-nitrophenylphosphonate, as the two had well-separated peaks. Diisopropyl o-nitrophenylphosphonate and ethyl o-nitrophenylmethylphosphinate formed overlapping peaks with dibutyl phthalate. For the former, fluorene was used as internal

marker, while for the latter dimethyl phthalate was used.

Each tube was analysed three times, the tubes being kept at -20° in between analyses. Each run at a particular temperature consisted of 6-10 tubes. Rates were measured by following the rate of formation of product, the reaction being allowed to go as far as 20% formation of product; above this point deviations from straight-line plots were observed (see Discussion). Rate constants were determined graphically using the integrated second-order rate equation with varying initial concentrations of reactants. Good straight lines were realised. Values of the energy of activation were determined from an Arrhenius Plot of rate constants determined at five different temperatures. Values of the entropy of activation were calculated by the equation of Schaleger and Long [33] (d):-

$$k_2 = eK/h.T.\exp(\Delta S/R^{\ddagger}).\exp(-E_{act}/RT) \qquad (d)$$

k_2 = second-order rate constant

$\frac{eK}{h}$ = a composite constant for reactions in solution of value $5.665 \times 10^{+10}$ deg^{-1} sec^{-1}

T = absolute temperature

R = gas constant.

Product Analysis

A preliminary investigation confirmed the "cleanness" of the

reaction of triethyl phosphite and o-dinitrobenzene in acetonitrile. A kinetic run with a 20-fold excess of triethyl phosphite exhibited pseudo-first order kinetics with respect to o-dinitrobenzene at 78°. Analysis of the reaction mixtures of o-dinitrobenzene with triethyl phosphite and diethyl methylphosphonite by g.l.c. (Pye 104 chromatograph, flame ionization detector) showed only two peaks attributable to the reactant and product. In both cases some oxidation of the tervalent phosphorus compound occurred and in the case of triethyl phosphite, an upper limit of 25% triethyl phosphate was estimated for complete reaction of o-dinitrobenzene (Table 1).

One ml. samples of an acetonitrile solution of o-dinitrobenzene and triethyl phosphite (mole ratio 1:1.93) with hexamethylbenzene as marker were sealed in pyrex test-tubes and incubated at 86° for known periods of time.

The tube contents were analysed using the Pye 104 chromatograph, 2% NPGS column at 118°. The areas were measured by a Kent Chromalog Series I digital integrator and the head response was calibrated with mixtures of triethyl phosphate and hexemethylbenzene of known mole ratio (Table 1). The quantity of triethyl phosphate originally present in the sample of triethyl phosphite was determined by the same technique and its value subtracted from the measured reaction quantities.

TABLE 1: Formation of Triethyl phosphate during the Reaction of o-Dinitrobenzene with Triethyl phosphite in Acetonitrile

No. of hours heated	1	2	3	4¼	6½
Formation of phosphate (%).....	15	17	23	25	25

In a control experiment, samples of a standard solution of triethyl phosphite and hexamethylbenzene were heated for comparable times at 114° and the peak area ratios measured by g.l.c. under the previous conditions (Table 2).

TABLE 2: Formation of Triethyl phosphate during Handling and Heating of Solutions of Triethyl phosphite

No. of hours heated.....	½	1	1½	2	2½
Formation of phosphate (%).....	5	8	15	30	27

It was thus seen that considerable care would have to be taken to minimise atmospheric oxidation of the tervalent phosphorus compound during the time that it was handled in weighing and pipetting operations. Oxidation was kept to a minimum by working rapidly and maintaining a nitrogen atmosphere over the solutions.

Internal Marker Stability

The stability of the internal markers to tervalent phosphorus compounds in acetonitrile at the temperatures used was checked. Solutions containing triethyl phosphite (3.2286 g. in 25 ml., 19.4 M),

fluorene (0.3034 g. in 25 ml., 1.84 M), and dibutyl phthalate (2.012 g. in 25 ml., 7.5 M) in acetonitrile were heated under the experimental conditions at 87.50°. The ratios of the fluorene:ester peak areas were measured by the D.6 g.l.c. technique described, and are tabulated below (Table 3).

TABLE 3: Variation of Fluorene: Dibutyl phthalate Peak Area Ratios with Time

No. of hours heated.....	0	$2\frac{1}{2}$	4	$9\frac{1}{4}$	20	$46\frac{1}{4}$	$92\frac{1}{4}$
Peak area ratio.....	0.133	0.125	0.126	0.124	0.122	0.127	0.122

The ratios remained sensibly constant and it was concluded that both fluorene and dibutyl phthalate were inert to triethyl phosphite under the reaction conditions.

Rate Constants

The rate of formation of the products followed second-order kinetics, being first-order with respect to each reactant.

Rate constants (in duplicate) obtained for the reactions of tervalent phosphorus compounds with o-dinitrobenzene in acetonitrile are tabulated below (Tables 4, 5 and 6).

TABLE 4: Reaction of Trialkyl phosphites with o-Dinitrobenzene at 98.07°

R in R_3P	Conc.^{h} o-dinitrobenzene (moles $l.^{-1}$)	Conc.^{h} phosphite (moles $l.^{-1}$)	10^3 k_2 ($l.\ mole^{-1}\ min.^{-1}$)
MeO	0.2002	0.2007	2.75
MeO	0.1999	0.2007	2.72
EtO	0.2002	0.2005	12.1
Pr^iO	0.2001	0.2017	27.6
Pr^iO	0.2002	0.2017	27.0

TABLE 5: Reaction of Triethyl phosphite and o-Dinitrobenzene

Temperature	Conc.^{h} o-dinitrobenzene (moles $l.^{-1}$)	Conc.^{h} phosphite (moles $l.^{-1}$)	10^3 k_2 ($l.\ mole^{-1}\ min.^{-1}$)
57.43°	0.1995	0.1998	0.75
57.43	0.1995	0.1998	0.75
67.90	0.2021	0.2019	1.75
67.90	0.2022	0.2019	1.78
78.42	0.2018	0.2017	3.62
78.42	0.2021	0.2017	3.40
87.50	0.2005	0.1931	5.97
87.50	0.2000	0.3890	5.97
98.05	0.2018	0.2017	12.3
98.05	0.2000	0.1023	12.6

TABLE 6: Reaction of Diethyl methylphosphonite with o-Dinitrobenzene

Temperature	Conc.^{h}. o-dinitrobenzene (moles $l.^{-1}$)	Conc.^{h}. phosphonite (moles $l.^{-1}$)	10^{3} k_{2} ($l.\ mole^{-1}\ min.^{-1}$)
15.30°	0.2002	0.2008	3.51
15.30	0.2002	0.2008	3.44
25.00	0.2013	0.2019	6.88
25.00	0.2013	0.2019	6.95
31.84	0.2006	0.2006	10.8
31.84	0.2006	0.2006	10.9
40.20	0.2024	0.2029	21.2
40.20	0.2024	0.2029	21.6
50.10	0.2006	0.2001	40.3
50.10	0.2002	0.1016	39.8

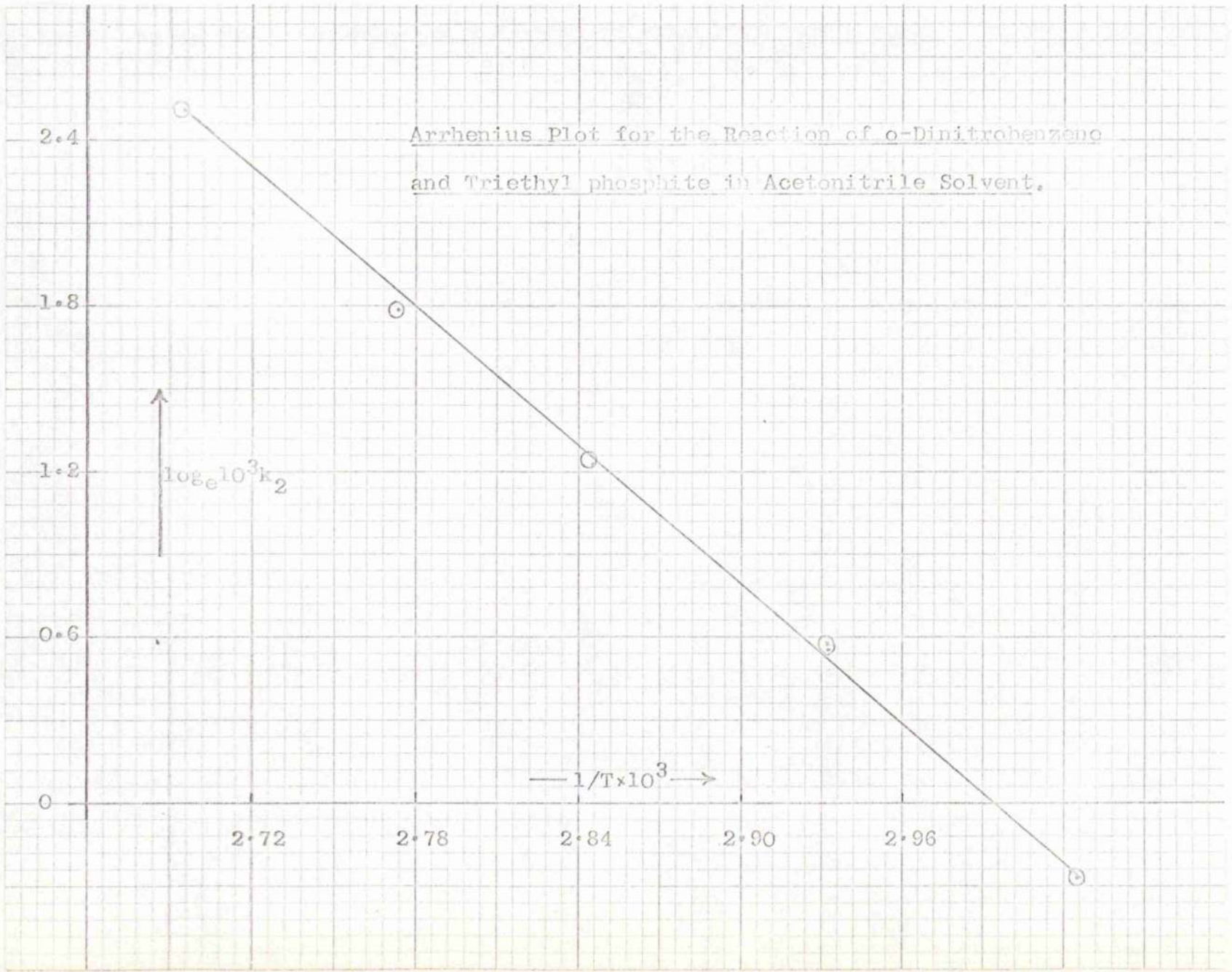
Using the rate constants in Tables 5 and 6, the results presented in Tables 7 and 8 were used for Arrhenius plots to determine the energies of activation.

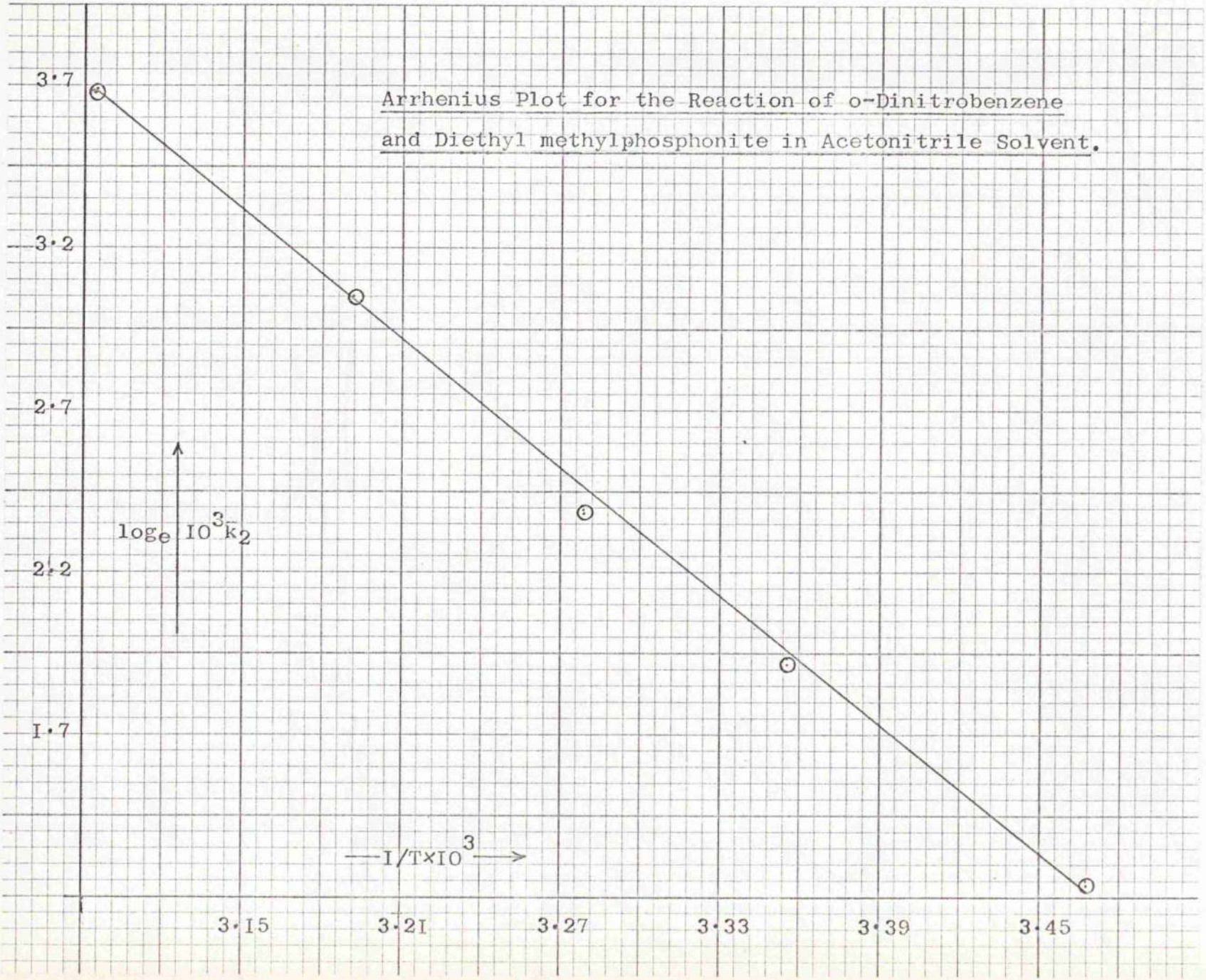
TABLE 7: Variation of Rate Constant with Temperature for o-Dinitrobenzene and Triethyl phosphite in Acetonitrile

$10^3 k_2$	Temp. ^oC	Temp. ^oA	$10^3 T^{-1}$	$\log_e 10^3 k_2$
0.75	57.4	330.4	3.026	-0.2864
1.75	67.9	340.9	2.933	0.5596
1.78	67.9	340.9	2.933	0.5766
3.62	78.4	351.4	2.846	1.2865
3.40	78.4	351.4	2.846	1.2238
5.97	87.5	360.5	2.774	1.7867
12.3	98.1	371.1	2.695	2.5096
12.6	98.1	371.1	2.695	2.5337

TABLE 8: Variation of Rate Constant with Temperature for o-Dinitrobenzene and Diethyl methylphosphonite in Acetonitrile

$10^3 k_2$	Temp. ^oC	Temp. ^oA	$10^3 T^{-1}$	$\log_e 10^3 k_2$
3.51	15.3	288.3	3.468	1.2556
3.44	15.3	288.3	3.468	1.2355
6.88	25.0	298.0	3.356	1.9286
6.95	25.0	298.0	3.356	1.9387
10.9	31.8	304.8	3.280	2.3888
10.8	31.8	304.8	3.280	2.3796
21.2	40.2	313.2	3.193	3.0540
21.6	40.2	313.2	3.193	3.0727
40.3	50.1	323.1	3.095	3.6964
39.8	50.1	323.1	3.095	3.6839


Arrhenius Plot for the Reaction of o-Dinitrobenzene and Triethyl phosphite in Acetonitrile Solvent.
2·4
1·8
1·2
0·6
0
$\log_e 10^3 k_2$
$-1/T \times 10^3 \rightarrow$
2·72
2·78
2·84
2·90
2·96


Arrhenius Plot for the Reaction of o-Dinitrobenzene
and Diethyl methylphosphonite in Acetonitrile Solvent.
3·7
3·2
2·7
2·2
1·7
$\log_e 10^3 k_2$
$1/T \times 10^3$
3·15
3·21
3·27
3·33
3·39
3·45

Values of the energies of activation and calculated results from them are summarised in Table 9.

TABLE 9: Experimental Activation Energies and Calculated Entropies of Activation

o-dinitrobenzene and R_3P	E_{act} (Kcals. $mole^{-1}$)	Temp. Range	Values of k_2 at 25.0°	$\Delta S^{\ddagger}$ 25.0°(e.u.)
R_3P, triethyl phosphite	16.0	57-98°	0.15×10^{-3}*	-32.1
R_3P, diethyl methylphosphonite	13.0	15-50°	6.93×10^{-3}	-34.9

* extrapolated.

The rate constants are estimated to have an accuracy of ± 5%. The error in measuring the gradient for the value of E_{act} is again estimated to be 3%. The value of the calculated entropy of activation, $\Delta S^{\ddagger}$, has a statistical error of the order of ± 1 e.u.

The Reaction of Dimethyl o-nitrophenylphosphonate with Trimethyl phosphite

An authentic sample of tetramethyl phenylene bisphosphonate was prepared by the method of Griffin and Obrycki.[6b]

One ml. of solution of fluorene (0.2831g.) and trimethyl phosphite (0.7498g.) in acetonitrile (made up to 10 ml.) and one ml. of solution of dimethyl o-nitrophenylphosphonate (0.6012g.) in

acetonitrile (10 ml.), were sealed in a pyrex test-tube, heated at 87.5°, and analysed at intervals by g.l.c. under the previously described conditions. The molar ratio of phosphonate:phosphite was 1:2·3. Values of the phosphonate:fluorene peak area ratio are tabulated (Table 10).

TABLE 10: Values of Phosphonate:Fluorene Peak Area Ratio

Time (hr.)	0	65	137	173	257	336
Phosphonate:fluorene peak area ratio	2.24*	1.80	1.69	1.79	1.72	1.63

(* calculated by weight)

No evidence for the formation of the phenylene bisphosphonate was observed on the g.l.c. trace for these anlayses by comparison of the chromatograms with that of the authentic sample. Trimethyl phosphate was detected in the mixture by operating the column at 90°.

Tetramethyl phenylene bisphosphonate, an internal marker dibutyl phthalate, and trimethyl phosphite in acetonitrile were heated at 86°. After 94 hours, the ratio of the peak areas of the bisphosphonate:marker were the same as before the heating had commenced.

Stability of Nitroethane and Amyl nitrite to Triethyl phosphite

The concentrations of nitroethane and amyl nitrite were followed by u.v. spectroscopy after incubation (98.07^{o}) under the reaction conditions with triethyl phosphite in acetonitrile. Amyl nitrite (b.p. 104^{o}) was used in preference to ethyl nitrite (b.p. 17^{o}) because of its lower volatility.

Triethyl phosphite and triethyl phosphate were shown to be optically transparent in the region 265-350 nm. Acetonitrile started to absorb strongly at 285 nm. and to show a maximum at 273.5 nm. Nitroethane ($c = 2.62 \times 10^{-2}$ moles $l.^{-1}$) showed a maximum at 276 nm. ($\varepsilon_{max} = 25.4$) in acetonitrile containing triethyl phosphite (0.06 mole/100 moles solvent). Amyl nitrite ($c = 2.78 \times 10^{-2}$ moles $l.^{-1}$) showed the characteristic range of absorptions [34a] for nitrites over the range 340-400 nm., one of the maxima being at 334 nm. ($\varepsilon_{max} = 58.4$) in acetonitrile containing triethyl phosphite (0.06 moles/100 moles solvent).

Solutions in acetonitrile containing triethyl phosphite (0.5120 g.) and nitroethane (0.0490 g.) made up to 25 ml. (abbreviated to "nitroethane reaction"), nitroethane (0.0504 g.) only made up to 25 ml. (abbreviated to "nitroethane blank"), amyl nitrite (0.0813 g.) and triethyl phosphite (0.5194 g.) made up to 25 ml. (abbreviated to "amyl nitrite reaction"), and amyl nitrite

(0.0578 g.) only made up to 25 ml. (abbreviated to "amyl nitrite blank") were maintained at 98.07° and the absorbance determined in matched cells at intervals of time paralleling the reaction rate of triethyl phosphite and o-dinitrobenzene.

The nitroethane solutions were analysed directly, while the amyl nitrite solutions were diluted by a factor of five. The values recorded are tabulated in Table 11.

TABLE 11: Absorbances Recorded for Amyl nitrite and Nitroethane with Triethyl phosphite in Acetonitrile at 98.07°

Amyl nitrite reaction:-	Time (mins.)	0	51	234	299	360
	Absorbance	0.311	0.281	0.332	0.318	0.311
Amyl nitrite blank:-	Time (mins.)	0	51			361
	Absorbance	0.298	0.318			0.340
Nitroethane reaction:-	Time (mins.)	0	64	145	235	300
	Absorbance	0.670	0.628	0.620	0.634	0.618
Nitroethane blank:-	Time (mins.)	0	65			359
	Absorbance	0.590	0.590			0.597

Formation of Nitroethane as a Reaction Product

Nitroethane (b.p. 114°) was observed to lie in the solvent tail of acetonitrile (b.p. 82°), when separated by g.l.c. using a 2% NPGS column at 24° on a Pye 104 chromatograph. Higher boiling solvents, benzonitrile and dimethyl formamide, were then used so

as not to obscure any separation of the nitroethane on the chromatogram.

In each solvent (25 ml.), o-dinitrobenzene (9.2 g., 55 m. moles) and triethyl phosphite (11.6 g., 70 m.moles) were dissolved and heated for 8 hours at 90° (D.M.F.) and 11 hours at 90° (benzonitrile) under a nitrogen atmosphere. In neither case was there any evidence of nitroethane formation by comparison of the reaction mixture chromatograms with that of authentic nitroethane. Besides the solvent peaks, the only other peaks observable were due to starting material and product.

Dealkylation of Triethoxy ethylphosphonium Fluoroborate

Triethyloxonium fluoroborate was prepared by the method of Meerwein.[35] Epichlorhydrin (b.p. 118°) and boron trifluoride etherate (b.p. 52-56°/18 mm.) were distilled before use. In the distillation of the latter, the precautions of Zweifel and Brown[36] were followed. Triethyloxonium fluoroborate was filtered off, washed with dry ether, and dried by passing dry nitrogen through it contained in a dry-box (m.p. 87-88° [sealed tube]. Meerwein[35] reported 92° [dec.]).

Triethoxy ethylphosphonium fluoroborate was prepared by Dimroth and Nürrenbach's method.[37] Triethyloxonium fluoroborate

(15 g., 79 m.moles) in dry methylene chloride (50 ml.) was treated with triethyl phosphite (14.8 g., 89 m.moles, 15.5 ml.). The solution became warm and after allowing it to stand for 10 minutes, the addition of ether (250 ml.) precipitated a colourless oil, which was separated and transferred to a 100 ml. multi-necked flask. Nitrogen was blown over the oil, while it was being magnetically stirred and warmed to remove the solvents.

Dealkylation by nitrite ion was performed in two solvents, one involatile to observe the volatile products of the reaction and the other comparatively volatile to observe involatile products. These solvents were benzonitrile and acetonitrile respectively.

(i) <u>In benzonitrile</u>:- Triethoxy ethylphosphonium fluoroborate (21 g., 75 m.moles) with silver nitrite (12.3 g., 80 m.moles) were kept at 80° for 3½ hours in benzonitrile (80 ml.). Nitrogen was passed at a slow rate over the mixture collecting the volatile products in a cold trap. The mixture was protected from light by wrapping in aluminium foil.

When the contents of the trap were allowed to warm to room temperature, the colour changed through a succession of colours, deep blue, light blue, and finally green with faint brown fumes being evolved. The colour changes are similar to those described for the behaviour of nitric oxide under such circumstances.[38]

Vogel [31b] has described the evolution of oxides of nitrogen during the reaction of bromobutane with silver nitrite. It is thus likely that the colour change is due to the presence of some nitric oxide trapped out from the reaction. The remaining liquid was kept at -20° for 12 hours over molecular sieve and then distilled into a second receiver. Yield 3 g., 40 m.moles, 52% assuming the compound is ethyl nitrite.

Analysis of the reaction mixture by g.l.c. (Pye 104, 2% NPGS, 24°) showed small amounts of volatile components, but none corresponding to nitroethane. This was confirmed by atmospheric distillation up to 160°. A few drops only of liquid condensed on the thermometer bulb and these were shown to be predominantly benzonitrile by its infrared spectrum ($\nu C{\equiv}N$, 2240 $cm.^{-1}$, compared with an authentic sample). More particularly, no absorptions were observed at 1372 or 1555 $cm.^{-1}$ (position of nitro-absorption for nitroethane).

(ii) <u>In acetonitrile</u>:- Triethoxy ethylphosphonium fluoroborate (17 g., 60 m.moles) and silver nitrite (12.3 g., 80 m.moles) in acetonitrile (50 ml.) were maintained at gentle reflux for 3 hours. The volatile products were collected, dried, and distilled as above to give 2 g. liquid, 27 m.mole, 45% assuming the compound is ethyl nitrite.

The distilled liquid from both experiments was identified as

ethyl nitrite by its b.p. 17°, its identical and superimposable i.r. spectrum to that of an authentic sample,[34b] and its characteristic, identical u.v. spectrum in ethanol,[34a] λ_{max} (nm.)359.0, 345.5, 329.5, and 315.5.

The reaction mixture showed only a small g.l.c. peak due to diethyl ethylphosphonate. After removal of the acetonitrile at atmospheric pressure, distillation at 18 mm. yielded a colourless oil (0.6 g.), which was shown to be predominantly diethyl ethylphosphonate (3.6 m.moles, 6%) by comparison of its i.r. spectrum with that of an authentic sample. Distillation of the residue yielded no further products. The i.r. spectrum of the residue showed massive absorptions at 1200-950 $cm.^{-1}$ as well as at 2,940 and 3,000 $cm.^{-1}$ (νC-H).

Both nitrite ion, P=O, and P-O - Et show strong absorption frequencies[39] in the region 1200-950 $cm.^{-1}$

The Reaction of Diethyl ethylphosphonate with Silver nitrite in Benzonitrile

Diethyl ethylphosphonate (8.7 g., 52.5 m.moles) and silver nitrite (8.2 g., 53 m.moles) were kept in benzonitrile (50 ml.) at 80° for 3½ hours. Volatile products were trapped as before. At the end of this time, the contents of the trap exhibited the colour

changes described earlier and contained ethyl nitrite (0.4 g., 5.35 m.moles, 10%) as shown by comparison of its i.r. and u.v. spectra with those of an authentic sample. The nature of the dealkylation products was not investigated.

DISCUSSION

The results in the experimental section point to the occurrence of nucleophilic aromatic substitution in the reactions of o-dinitrobenzene with tervalent phosphorus compounds. The major features of nucleophilic substitution have been discussed in the Introduction to this part of the thesis. The purpose of this Discussion will be to indicate how the title reaction can be accommodated with these features.

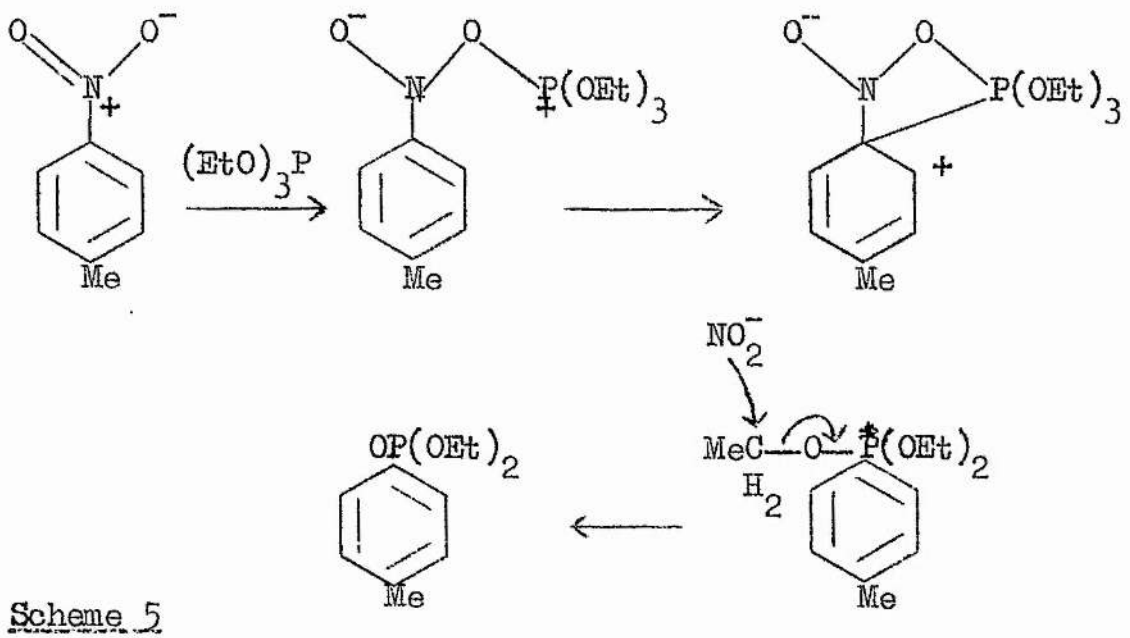
The preparative work of Cadogan and his co-workers [1b] showed that those substrates which gave good yields of substitution products were those containing groups accepted to activate nucleophilic substitution.

The alternative mechanism of electrophilic attack at the aromatic ring appears to have been realised in the work of Cadogan, Sears and Smith, [40] who obtained diethyl arylphosphonates in low yield by refluxing p-alkyl and p-alkoxyl nitrobenzenes with triethyl phosphite. Among the other products formed by deoxygenation of the nitro group, there was also 3-5% of nitro group displacement. The compounds obtained and their yield, estimated by g.l.c., are tabulated (Table 12).

TABLE 12: Yield of Arylphosphonates from Nitro-compounds with boiling Triethyl phosphite

Substituted nitrobenzene.....	p-Me	p-Et	p-OMe	o-OMe
Yield of phosphonate (%).....	5-7	5	6	2·5

The mechanism suggested by these workers involves an initial nucleophilic attack on the oxygen atom of the nitro group creating an electrophilic phosphorus atom. The phosphorus atom is then free to move into a position such that electrophilic attack on the aromatic ring occurs with the formation of a four-membered intermediate. This intermediate then collapses to lead to the observed products (Scheme 5).



Scheme 5

The formation of phosphonates by this mechanism occurred only with substituents which favour electrophilic attack by helping to

stabilise the positive charge developed on the ring.

It is significant that no substitution products were observed with p-dinitrobenzene.[1b] The aromatic ring is deactivated with respect to electrophilic substitution and no phosphonate product was observed in accord with the four-centre mechanism shown in Scheme 5.

Where phosphonate formation is the only reaction occurring, the effective substituents are those which direct nucleophilic substitution. Electrophilic mechanisms involving nucleophilic attack on nitro-group oxygen to form electrophilic phosphorus would appear to be discounted in view of the ring deactivated towards electrophilic substitution and the inability of p-dinitrobenzene to form any phosphonate products.

The values of the activation parameters for triethyl phosphite (E_{act} 16.0 Kcals./mole, $\Delta S^{\ddagger}$ -32.1 eu) and diethyl methylphosphonite (E_{act} 13.0 Kcals./mole, $\Delta S^{\ddagger}$ -34.9 eu) with o-dinitrobenzene indicate the same rate-determining step for both compounds. The observed second-order kinetics, first order in each reactant, are in agreement with a bimolecular mechanism. The entropies of activation are similar, the greater reactivity of diethyl methylphosphonite being due to the lower activation energy (ΔE_{act} 3 Kcals./mole).

The observed value of ΔE_{act} is similar to that reported by

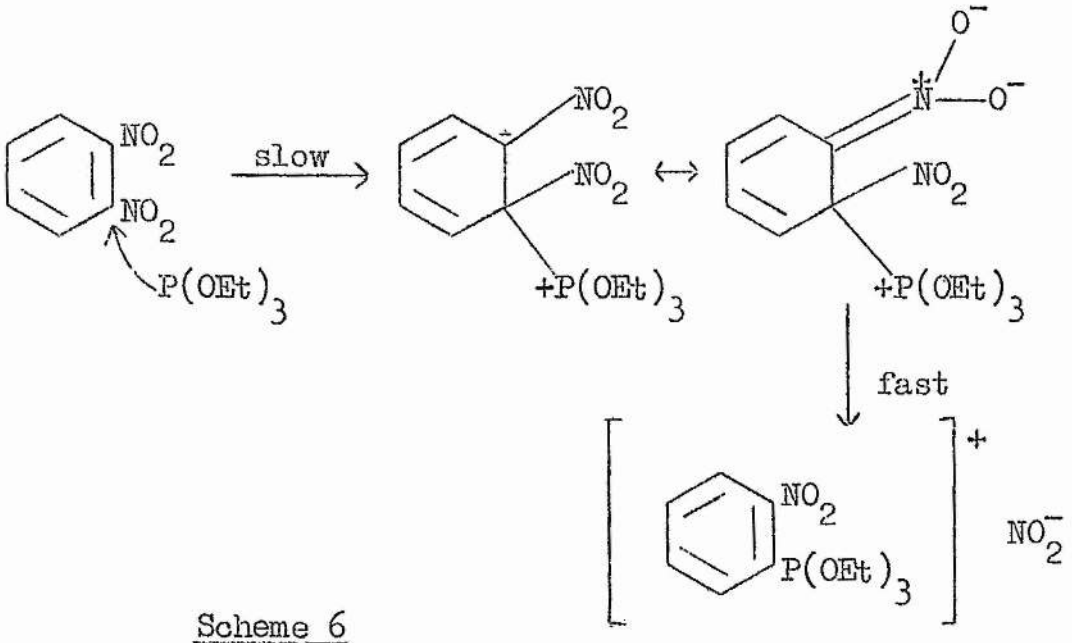
Aksnes and Aksnes[41] on the Arbusov reaction between phosphorus nucleophiles and ethyl iodide (Table 13). They gave values of ΔE_{act} of 4.1 Kcals./mole and 2.9 Kcals/mole for the successive replacement of ethoxyl group by phenyl from triethyl phosphite. It is established[42] that the Arbusov reaction proceeds via a rate-determining initial step of attack of the phosphorus nucleophile on the alkyl halide. The similarity in the reactivity order

TABLE 13: Activation Parameters for Phosphorus Nucleophiles with Ethyl Iodide

Phosphorus Nucleophile	$10^4 k_2$ (60°) (l.mole^{-1}sec.$^{-1}$)	E_{act} (Kcals./mole)	$\Delta S^{\ddagger}$ (e.u. 60°)
$(EtO)_3P$	0.19	21.0	-19.4
$(EtO)_2PPh$	1.65	16.9	-27.4
$(EtO)PPh_2$	2.47	14.0	-35.4

of triethyl phosphite and diethyl methylphosphonite towards ethyl iodide and o-dinitrobenzene indicates the same rate-determining step. Nucleophilic attack by phosphorus yields an intermediate Meisenheimer-type complex, which regains aromaticity by ejection of nitrite ion to form a quasi-phosphonium salt (Scheme 6).

The change in the entropy of activation for the two phosphorus nucleophiles towards o-dinitrobenzene is also significant when compared to the change $\Delta\Delta S^{\ddagger}$ in the reaction with ethyl iodide. Aksnes[41] proposed an explanation of the decreasing entropy of

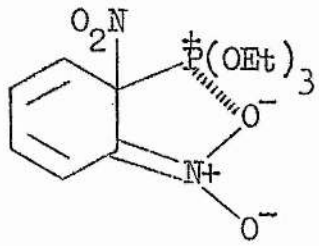


Scheme 6

activation with increasing ethoxyl substitution as reflecting the degree of electromeric (+M) stabilisation by the ethoxyl groups, with a consequent decrease in the need for solvation of the intermediate phosphonium ion. Less ordering of the solvent is necessary, which results in a lower activation entropy (Table 13).

In both Aksnes' investigations[41] and the present work a common solvent, acetonitrile, was used and the smaller change in entropy $\Delta\Delta S^{\ddagger}$ for the reactions of triethyl phosphite and diethyl methylphosphonite with o-dinitrobenzene can be taken to indicate the involvement of an alternative interaction, which decreases the need for solvent interaction and consequent orientation. This interaction could be the simple electrostatic interaction of the positive phosphonium centre and the negative charge carried by the oxygen atoms of the neighbouring nitro group (16). This provides

a direct analogy to the suggestion of Bunnett and Morath[24] of "built-in solvation" (17).



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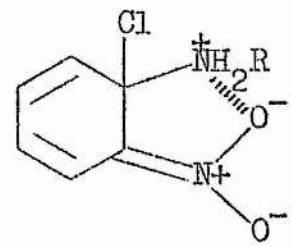


(17)

Their work was directed towards providing an explanation of the ortho:para ratios observed with amine attack on o-halonitroaromatics. For the amines the explanation more probably involves hydrogen bonding,[14,23] but the intermediate (16) might provide the first example of "built-in solvation".

This "built-in solvation" will help the formation of the transition state where the leaving group is ortho to a nitro group. Nucleophilic substitution with tervalent phosphorus reagents occurred with those compounds that possessed leaving groups ortho to the nitro group, but failed with p-dinitrobenzene where stabilization by "built-in solvation" is not possible.

The rate constants establish the empirical observations of Cadogan et al.,[1b] who observed for the reaction of o-dinitrobenzene and various tervalent phosphorus compounds the reactivity sequence

Ph_2POEt > $(EtO)_2PMe$ > $(EtO)_3P$. More interestingly, the order for trimethyl and triethyl phosphites as commonly expressed [7] is reversed, but the greater reactivity of triisopropyl phosphite than triethyl phosphite is confirmed. Thus, the reactivity order for o-dinitrobenzene substitution by trialkyl phosphites is Pr^iO > EtO > MeO.

Kabachnik [7] quoted the series for tervalent phosphorus nucleophilicity with particular reference to the Arbusov reaction and gave the reactivity series of R_3P as following alkyl > aryl > alkoxy and MeO- > EtO- > PrO- > BuO- substituents.

Although the nucleophilicity is controlled by the inductive effects of the substituents, steric factors have also to be considered in the overall reactivity.

The large increase in nucleophilicity of triisopropyl phosphite by the increased inductive effect (+I) of the alkyl groups is countered by the lower frequency factor in the Arbusov reaction with ethyl iodide. Aksnes [43] showed that triisopropyl phosphite reacted at only twice the rate of triethyl phosphite, although the activation energy of the former was 4.5 Kcals./mole lower. The increase in nucleophilicity was compensated for by a considerably lower frequency factor ($10^{2.5}$), which was a measure of the degree of steric interaction between the substrate and the bulkier phosphite.

The qualitative series of Kabachnik[7] for the phosphite reactivity in the Arbusov reaction is also affected by the steric requirements. Increasing alkyl substitution after triethyl phosphite has little effect on the nucleophilicity of the phosphorus atom because of the attenuation of the inductive effect through two carbon atoms. The rates do in fact decrease, and this can be taken as increasing steric inhibition by the bulkier alkyl groups.

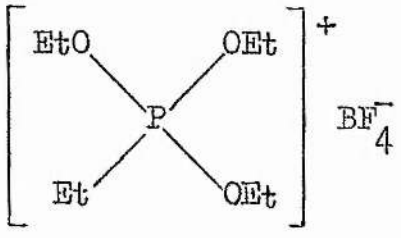
The inversion of triethyl and trimethyl phosphites in their reactivity towards o-dinitrobenzene compared with the Arbusov reaction could result from the increased nucleophilicity of triethyl phosphite which is not matched by a decrease in the frequency factor. The overall small change in rate and the relatively large opposite changes in the activation energy and entropy of triisopropyl phosphite and ethyl iodide show that such an inversion in rate is possible under some circumstances.

The final phosphorus-containing product is obtained by dealkylation of the intermediate (16) by the nitrite ion. It is generally agreed that the dealkylation of the quasi-phosphonium salt is non-rate-determining in the Arbusov reaction. The reaction of triethyl phosphite and ethyl iodide was investigated by Aksnes[41] who showed, in support of a non-rate-determining dealkylation stage, that the ethyl iodide was not measurably consumed during the

reaction and that the rate was unaffected by added iodide ion.

A similar conclusion is reached from Gerrard and Green's[44] kinetic study of the dealkylation of phosphorus esters. The dealkylation was shown to be bimolecular. A rate-determining S_N2 dealkylation step in the quasi-phosphonium intermediate would require that secondary alkyl phosphites react more slowly than primary alkyl phosphites. The observed facts are contrary to this, and so the dealkylation cannot be rate-determining.

The existence of a quasi-phosphonium salt is quite well established in the Arbusov reaction. Dimroth and Nürrenbach[37] prepared an alkoxyl phosphonium salt (18) under anhydrous conditions by ethylation of triethyl phosphite with triethyloxonium fluoroborate. The compound was a 1:1 electrolyte in acetonitrile and could be dealkylated by propoxide ion in propanol to the corresponding phosphonate ester and ethyl propyl ether. A number of workers[42] have reported physical evidence which is claimed to establish either that the reaction proceeds in two distinct stages, or that discrete intermediates are formed.



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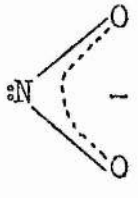


(19)

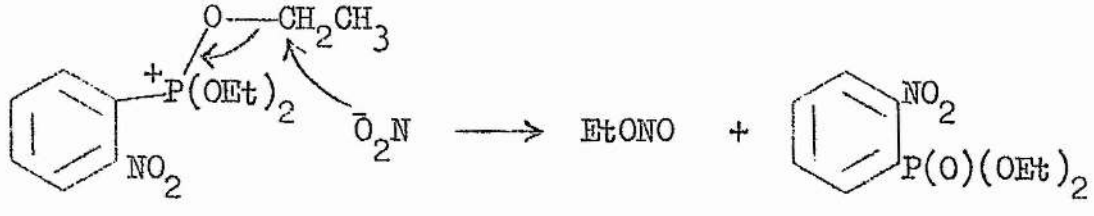
The nitrite ion (19) is an ambident ion, that is, nucleophilic attack by oxygen or nitrogen may occur. Gompper[45] considered the question of ambident ion reactions by distinguishing between thermodynamically and kinetically controlled reactions and the circumstances which would cause one of these to predominate. Kornblum and co-workers[46] have examined the more restricted case of the alkylation of nitrite ions. From their results they proposed that the greater the carbonium ion character of the transition state, then the greater is the tendency for covalency formation to the atom of greater electronegativity to form alkyl nitrites. Electrophilic interaction by silver on the halogen atom of the alkyl halide substrate greatly increased the yield of alkyl nitrites by increasing the carbonium ion character of the transition state.

This generalisation is of value in the present work as it provides an explanation of the absence of nitroethane as a reaction product from the dealkylation of the quasi-phosphonium intermediate. A control experiment showed that the rate of consumption of nitroethane by triethyl phosphite under the reaction conditions was slower than the formation of diethyl o-nitrophenylphosphonate. Thus, there would be a high enough concentration of the nitroethane at the completion of the experiment to enable it to be detected by g.l.c. The complete absence of nitroethane in the mixture shows

that it is not formed during the reaction.

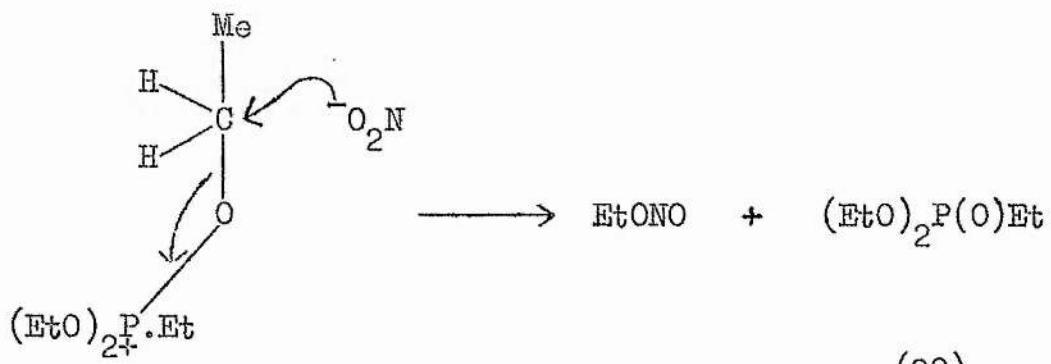
A common feature of organo-phosphorus chemistry is that the strength of the phosphoryl bond in the stability of the products controls the course of a reaction. The stability arises from p_{π}-d_{π} interactions with P^{+} acting as electron acceptor. Typical bond dissociation energies for phosphates and phosphine oxides[47] are 120-150 Kcals./mole, which are much higher than the corresponding values for amine oxides,[48] 50-70 Kcals./mole, where no such back bonding is possible.

By analogy to the Arbusov reaction, the dealkylation of the quasi-phosphonium nitrite formed in the reaction with o-dinitrobenzene with triethyl phosphite is not rate-determining. The formation of the phosphoryl bond provides electromeric assistance (-M) which creates large carbonium ion character in the transition state. Hence from Kornblum's generalisation,[46] only ethyl nitrite would be expected in the dealkylation by nitrite ions (Scheme 7).



Scheme 7

In a control experiment devised to create a quasi-phosphonium nitrite in situ, triethoxy ethylphosphonium fluoroborate (18) was allowed to react with silver nitrite in benzonitrile. Exclusive formation of ethyl nitrite (50%) occurred. The yield of the expected diethyl ethylphosphonate (20) was low (6%) and only part of the missing product was accounted for by further dealkylation of the phosphonate. While the dealkylation of triethoxy ethylphos-



(20)

Scheme 8

phonium nitrite (Scheme 8) to yield ethyl nitrite does not prove the intermediacy of Scheme 7, it does show that quasi-phosphonium nitrites do give rise to the exclusive formation of ethyl nitrite.

The experiments designed to measure the rate of consumption of nitroethane and amyl nitrite with triethyl phosphite under the reaction conditions showed that the rates of reaction were slow compared with the rate of formation of diethyl o-nitrophenylphosphonate. Amyl nitrite showed some instability under the reaction conditions, since the absorbance changed by 13% in 6 hours. The

nitroethane absorbance changed by 7% over 5 hours.

There have been few reports on the reactivity of aliphatic nitro-compounds with tervalent phosphorus compounds.[2] All of these have been concerned with halogenonitro-compounds. Simple nitroalkanes do not react with triphenyl phosphine at -10° and reactions at higher temperatures have not been investigated.[2] Boyer and Woodyard[49] have reported the deoxygenation of some organic nitrites with triethyl phosphite and their results indicate that the rate of reaction is again relatively slow. Benzyl nitrite was found to react to the extent of 70% with triethyl phosphite at 100° after two days, to yield benzyl alcohol (55%).

Triethyl phosphate (25%) was formed in the reaction of o-dinitrobenzene with triethyl phosphite in acetonitrile at 86° after 6½ hours. In a control experiment, where triethyl phosphite only was heated in acetonitrile, 15% of triethyl phosphate was formed in a comparable time (1½ hours) at 114°.

Such measurements of the extent of formation of triethyl phosphate are difficult because of the ease of oxidation of triethyl phosphite while it is weighed, handled, and heated. However, it is clear that the extent of formation of triethyl phosphate is quite low, possibly about 10% during the main reaction. This could arise from secondary deoxygenation reactions with the

products of the primary reaction, ethyl nitrite and diethyl o-nitrophenylphosphonate.

Boyer's and Woodyard's observations[49] and those of the current work indicate a slow reaction of nitrites with triethyl phosphite. Further slow deoxygenation of the primary product, dimethyl o-nitrophenylphosphonate, by trimethyl phosphite was also observed in the experiments designed to detect the formation of tetramethyl phenylene bisphosphonate.

The rate of formation of the primary product was observed to decrease slowly from that expected if second-order kinetics were still being obeyed, after about 20% of reaction. The importance of the secondary reactions increases as the concentrations of the products increase and it is possible that the deviation after 20% of reaction marks the increased competition from these secondary reactions.

The failure of diethyl o-nitrophenylphosphonate and p-dinitrobenzene to undergo substitution by triethyl phosphite is indicative of the importance of the neighbouring nitro group in determining the reactivity of o-dinitrobenzene, 2-nitropyridine -1-oxide, and 1,2,4-trinitrobenzene. Earlier in this discussion, it was suggested that the neighbouring nitro group helped by means of "built-in solvation".

A related enhancement of reactivity by a neighbouring N-oxide function was observed by Johnson[10] in his investigation of the substitution reactions of 2- and 4-substituted nitropyridine-1-oxides with piperidine or ethoxide ion. The activation energy for the reaction of 4-nitropyridine-1-oxide with piperidine in ethanol was 4.5 Kcals./mole higher than for the 2-isomer. Johnson believed this difference was due to the electrostatic interaction between the negatively charged oxygen atoms, which would raise the energy of the ground state for the 2-isomer relative to the 4-isomer. A further contribution to the lack of reactivity of the latter was the attenuation of the inductive effect of the N-oxide function at the 4-position. This idea would equally well apply to the dinitrobenzenes; electrostatic interaction raises the ground state energy of o-dinitrobenzene relative to the p-isomer in which full coplanarity of the nitro groups results in a greater degree of mesomeric stabilisation.

Cadogan and his co-workers[1b] showed that 2-nitropyridine-1-oxide underwent substitution with triethyl phosphite, whereas the 4-isomer failed to react. This is in accord with Johnson's observation of the greater activation energy of substitution for the 4-isomer. Substitution of the 4-isomer by triethyl phosphite fails because the activation energy is higher than that for deoxygenation which occurs by default.

By analogy, the lack of substitution by tervalent phosphorus compounds with p-dinitrobenzene results from similar effects: (a) the greater stability of the ground state, and (b) the lack of "built-in solvation", which result in higher activation parameters for substitution such that deoxygenation becomes the preferred reaction pathway.

It is a feature of the reactions reported by Cadogan[1b] that either substitution or deoxygenation occurred. The deoxygenations were generally performed in the absence of solvent at higher temperatures. It would then seem that the deoxygenation reaction has higher activation parameters than does substitution and in the absence of features facilitating nucleophilic aromatic substitution, deoxygenation then occurs by default of substitution.

In the case of dimethyl o-nitrophenylphosphonate, however, there was little further reaction by either substitution or deoxygenation. No substitution occurred but deoxygenation occurred over 15 days at 87°. It has been shown[9] that the p-nitro and p-diethyl phosphonyl groups have comparable electron-withdrawing capacities. In the absence of any other effect and making a statistical allowance for only one nitro group, further substitution should occur at a similar rate to yield a phenylene bisphosphonate. A control experiment showed that tetramethyl phenylene bisphosphonate was stable under the reaction conditions.

The lack of further substitution of dimethyl o-nitrophenylphosphonate is attributable to two causes: (a) the lack of "built-in solvation" between the neighbouring nitro group and the positive phosphonium centre, and (b) steric interactions. The retarding effects of large ortho groups were traced in the Introduction, where it was shown that strong steric inhibition was exhibited by the t-butyl group.[26] The diethyl phosphonyl group is also a bulky group and together with the size of the attacking nucleophile, triethyl phosphite, should provide strong steric hindrance to further substitution. Steric hindrance might also be responsible for the stability of the nitro group towards deoxygenation, since in general complete deoxygenation[2] of aromatic nitro-compounds would normally have resulted under these conditions.

Conclusions

The work discussed in this part of the thesis has been concerned to establish whether nucleophilic aromatic substitution occurs in the reaction of o-dinitrobenzene with tervalent phosphorus reagents. The kinetic results, together with the work of Cadogan, Sears and Smith,[1] show quite clearly that this is so.

There is a fine balance between the customary deoxygenation

and substitution reactions. Where the substrate is insufficiently activated towards nucleophilic substitution, then deoxygenation occurs. The formation of phosphonates by those substrates with an o-nitro group results from the nucleophilic activation of the ring and the "built-in solvation" of the positive phosphonium intermediate.

Exclusive formation of ethyl nitrite in the dealkylation of the phosphonium intermediate is attributed to the high carbonium ion character of the transition state caused by the electromeric effect of the positive phosphorus centre. Preferred bond formation to the more electronegative atom of the nitrite ion then occurs.

The stability of the nitro group in diethyl o-nitrophenylphosphonate to trimethyl phosphite is attributed to strong steric shielding by the diethyl phosphonyl group.

P A R T I I

THE REACTIVITY OF THE ADDUCTS OF *p*-NITROBENZONITRILE OXIDE AND SOME PHOSPHORUS-CONTAINING ACIDS

ABSTRACT OF PART II

A series of alkyl α-hydroxyimino-p-nitrobenzyl alkylphosphyl adducts have been synthesised from phosphorus-containing acids and p-nitrobenzonitrile oxide. Their solvolytic behaviour has been examined.

Hydrolysis occurred in acid solution at 25° with anchimeric assistance of about 2×10^7 by the neighbouring oximino group, to yield the alcohol of the ester moiety. Exclusive phosphorus-oxygen fission occurred.

p-Nitroaniline was formed in alkaline solution by intramolecular attack by the oximate anion, followed by a Lossen rearrangement. Evidence is presented for the intermediacy of pentacovalent intermediates, and the relative reactivities of the adducts are explained by the constraints necessary for pseudo-rotation to allow further reaction to form the products in alkaline solution.

The acid hydrolysis of ethyl pinacolyl methylphosphonate was shown to proceed via a unimolecular mechanism with the formation of a carbonium ion in 50% aqueous dioxan at 100°.

CONTENTS OF PART II

Page No.

INTRODUCTION

Preamble

The great interest in organophosphorus compounds has develop. over the last thirty years. Three main factors have been responsible for this interest: the realisation of the importance of phosphorus esters in living processes, the great industrial uses made of phosphorus compounds, and the potential anti-acetyl cholinesterase activity of some phosphorus compounds.

Complex phosphorus esters play an essential rôle in the function of living processes and these, together with simpler phosphate ester systems, have been much studied.

Phosphorus compounds have been put to many industrial uses, some of which include antioxidants, lubricating oil and motor fuel additives, plasticisers, ligands in organo-metallic catalysts, and medicinals.

Some phosphorus compounds possess anti-acetyl cholinesterase activity and these have encouraged research into their development as war gases and more importantly as insecticides.

This thesis describes the synthesis and solvolytic behaviour of a model phosphonate ester system, in which a neighbouring oxime

group is able to provide anchimeric assistance in its hydrolysis. The relevance of such a system to the therapy of reactivation of inhibited acetyl cholinesterase will be traced in the Introduction.

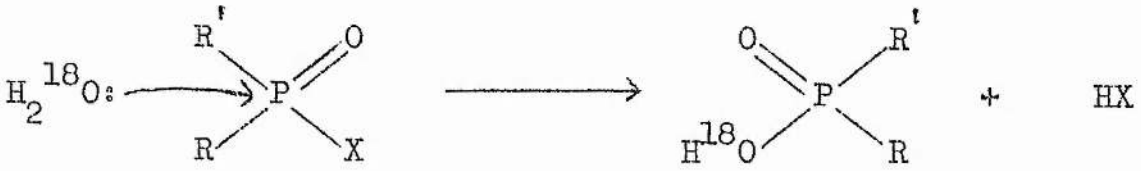
The Introduction will first deal with the acid and base hydrolysis of simple phosphonates, and with other phosphorus esters which exhibit neighbouring group participation in their hydrolyses. The rôle of the penta-coordinate intermediate will be discussed with regard to cyclic phosphorus esters and then to reactions which are capable of forming five-membered ring intermediates by initial intramolecular attack.

The Hydrolysis of Phosphonates: Hydrolysis Accompanied by Phosphorus-Oxygen Fission

Nucleophilic substitution at the phosphorus centre is thought to proceed through a five-coordinate transition state without the formation of a pentacovalent intermediate.[50]

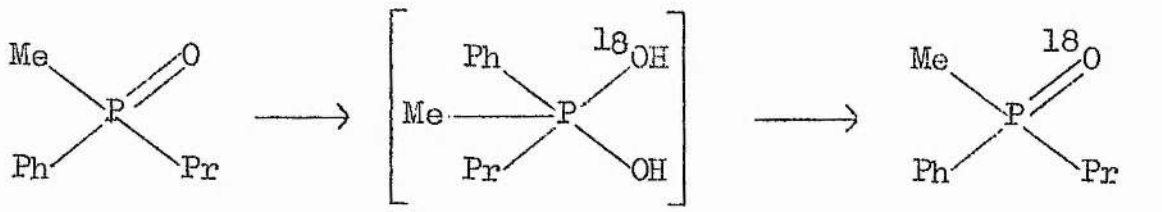
The most telling evidence against such an intermediate, in acyclic phosphorus ester hydrolyses, comes from oxygen exchange experiments. In the hydrolysis of chlorides, fluorides, and esters of phosphorus, only one atom of oxygen, ^{18}O, is found in the product and none in the starting material of an interrupted hydrolysis.[51a] More recently, lack of exchange has been reported in the hydrolyses of phosphinate esters.[52] A transition state is

required to be of form, to be compatible with these observations, thus:



Ring strain is believed to be responsible for increased ^{18}O exchange in cyclic five-membered esters, which proceeds via a pentacoordinate intermediate.[53] This will be returned to at a later point in this Introduction.

Some addition-elimination mechanisms are known for phosphorus compounds. A pentacoordinate intermediate (21) was probably formed in the slow exchange,[54] concomitant with racemization, with ^{18}O from enriched water in acid dioxan of the optically active phosphine oxide (20).



HCl, dioxan, $H_2{}^{18}O$, 55 days.

racemic, 0.87 atoms ^{18}O

(20) (21)

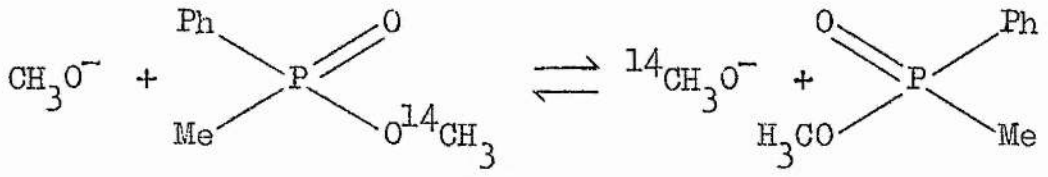
Many of the reactions of tetrahedral phosphorus compounds with nucleophiles are first-order in substrate and first-order in the

nucleophile. Amine[55,56] and hydroxide ion[57-60] displacements of the halide ion from phosphorus chlorides and fluorides and the hydrolyses of phosphonate esters[61-63] have been studied by many workers.

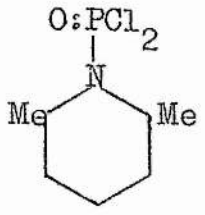
Alkaline ester hydrolysis activation parameters have been tabulated by Ginjaar and Basse-Vel[64] for p-nitrophenyl phosphorus esters, and by Christol and Marty[63] for symmetrical dialkyl alkyl-phosphonates. In most cases, the entropy terms obtained are large and negative, in harmony with a transition state which satisfies the requirements for synchronous attack by the nucleophile and ejection of the leaving group.[63,65]

Studies on the stereochemistry of the bimolecular displacement have so far indicated that inversion of configuration occurs. Hudson and Green[66] have conclusively demonstrated inversion in the equilibration of the optically active ^{14}C labelled phosphinate ester (22) with its unlabelled analogue in methanol. They found that the rate of racemization was exactly twice the rate of loss of labelled ^{14}C from the phosphinate ester. Thus, the ester must undergo displacement with inversion of configuration at phosphorus.

Some Polish workers have constructed Walden cycles for thiophosphorus compounds, in which each reaction involves bimolecular displacement at phosphorus.[67]



Attack at tetrahedral phosphorus is very susceptible to steric hindrance by substituents at the phosphorus atom.[61,63] A direct example arises from the ability of the phosphorochloridate (23) to phosphorylate only primary alcohols to give the corresponding phosphoroamidochloridate, while the less hindered derivative (24) phosphorylates all alcohols.[68]



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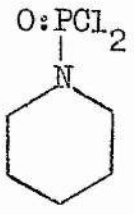

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Christol and Marty[63] have examined the effect of steric hindrance of the alkaline hydrolyses of some symmetrical dialkyl methylphosphonates. On increasing alkylation in the ester moiety the energy of activation increased as the electrophilicity of the phosphorus atom was reduced. The values of the entropy of activation increased regularly, reflecting the steric compression

in the transition state, where five groups surround the phosphorus atom. The secondary alkyl ester, dicyclohexyl methylphosphonate, was less reactive due to the increased energy and entropy of activation.

Substitution of the cyclohexyl group at phosphorus caused the rate of hydrolysis to fall in comparison with the corresponding methylphosphonate, due mainly to the inductive effect (Table 12).

On the other hand, the substitution of a phenyl group for methyl at phosphorus caused a rate increase, which resulted from the lower energy and entropy of activation. The planar ring must presumably cause a sufficient relaxation in the steric requirements compared with sp^3 hybridised carbon at phosphorus (Table 12).

TABLE 12: Rates of Alkaline Hydrolysis of $RPO(OMe)_2$ [63]

R	Relative Rate	E_{act} (Kcals./mole)	$\Delta S^{\ddagger}$ (e.u.)
Methyl	225	11.2	-21.2
Cyclohexyl	1	14.6	-21.7
Phenyl	380	11.7	-18.7

In a similar study of the alkaline hydrolyses of diisopropyl alkylphosphonates, Hudson and Keay [61] attributed the decreasing rate of reaction with increasing alkylation at phosphorus to steric effects. For the t-butylphosphonate, however, the reduced rate

$k_{Bu^t}/k_{Me} = 0.002$ is probably due to a combination of steric and inductive effects.

Most substituents at phosphorus exert a negative inductive effect on the phosphorus atom. This might have been expected to increase the rate of reaction by the increased electrophilicity of phosphorus. However, the increased electrophilicity in the first instance will increase the degree of $p_\pi - d_\pi$ bonding to the phosphorus atom, which causes changes in the energy and entropy of activation.

The rise in the activation energy for alkoxyl substituted compounds has been attributed to the increase in the π bond order in the molecule, which is caused by overlap of filled p orbitals of the substituents with the empty d orbitals of phosphorus. The resulting reduction of the positive charge on phosphorus, as well as the corresponding strengthening of the bond between phosphorus and the leaving group, contributes to an increase in the activation energy. There is a compensating effect in that the number of electronegative substituents bonded to phosphorus results in more efficient delocalisation of the electronic charge in the transition state. Accordingly, there is a reduced need for solvent orientation around the transition state, with a decrease in the entropy of activation.

Aksnes and Songstad[65] have reported rate constants for the alkaline hydrolysis of substituted diethyl alkylphosphonates, in which the inductive effect was studied. Concurrent with the lowering of the activation energy by inductive groups (-I), there was an increase in the infrared stretching frequency of the phosphoryl group, which was taken as evidence of the increased degree of $p_{\pi} - d_{\pi}$ bonding.

Potentially conjugative substituents can interact weakly among themselves through the d orbitals of the phosphorus atom. Electron release by substituents with lone pairs of p electrons does reduce the rate of reaction. Such effects have been experimentally determined by Hudson[58] and Aksnes.[69] Aksnes showed that increasing alkoxyl substitution in phosphorus fluoridates increased both the energy of activation and the degree of $p_{\pi} - d_{\pi}$ bonding to the phosphoryl group and fluorine atom (deduced from the rise in the infrared stretching frequency). Hudson and Keay[58] determined Arrhenius parameters for the solvolysis of phosphyl chloridates with similar steric requirements in 5% aqueous acetone (Table 13). The value of the activation energy increased with the degree of $p_{\pi} - d_{\pi}$ bonding available from methoxyl substitution. Values obtained from the alkaline hydrolysis[58] of some similar phosphyl esters also exhibit this effect thus:

Ester:	$Et_2P(O)OMe$	$EtP(O)(OMe)_2$	$P(O)(OMe)_3$
Relative rate per methoxyl group:	5.9	4.2	1

TABLE 13: The Effect of Methoxyl Group Substitution on some Phosphyl Chloridate Hydrolyses at 0°

Compound	$Et_2P(O)Cl$	Et.MeOP(O)Cl	$(MeO)_2P(O)Cl$
10^3k_1 ($sec.^{-1}$)	1500*	98	1.75
E_{act} (Kcals./mole)	7.3	8.4	10.6
$\log_{10}$ PZ	5.9	5.7	5.7

(* extrapolated)

These authors also attributed the decrease in rate with increasing alkylation in the ester moiety to the greater ease of electron release from the oxygen atom to phosphorus. It is also possible that steric effects are partially responsible for the decrease in the rate of hydrolysis. Phenoxide substituents showed less effect for their size, presumably because conjugation of the lone pair electrons on the oxygen atom with the aromatic ring allows the inductive effect of oxygen to predominate at the phosphorus atom.

The effect of the variation of the solvent on the rate of hydrolysis of tetrahedral phosphorus compounds has been studied by Hudson and Keay.[70] Phosphonochloridates were 10^3 less reactive when in formic acid containing 0.7% water than when in aqueous ethanol of comparable ionizing power. The rate of solvolysis also

increased in aqueous acetone mixtures, when the proportion of water was increased. They concluded that bond-formation rather than bond-breaking was the important factor in these hydrolyses.

Thus, the evidence summarised in the preceding paragraphs concerned with the effects of electronic interactions, the stereochemistry of the displacement, the lack of exchange with solvent, and the effects of the solvent indicate a bimolecular transition state[63,65] in the alkaline hydrolyses of phosphorus compounds.

Recently, it has been suggested that transient pentacoordinate intermediates may be involved in the reactions of a series of diisopropyl esters, $(Pr^{i}O)_2P(O)X$.[71] The rate of phosphorylation follows the basicity of the nucleophile, which suggests strong interaction in the transition state. Hudson and Greenhalgh[71] explained the relative reactivities of the nucleophiles, $H\bar{O}$, H_2O, and $BuNH_2$ towards $(Pr^{i}O)_2P(O)X$ [X=F, Cl, CN, and $OP(O)(OPr^{i})_2$] in terms of the relative leaving group tendencies of the attacking nucleophile in a pentacovalent intermediate.

The Nature of the Attacking Nucleophile

The characteristics of nucleophiles have been discussed by Edwards and Pearson[72] in terms of three parameters: basicity, polarisability, and the α-effect. Electrophilic centres were then

classified in terms of which of these factors was important in the transition state.

For the phosphorus atom the available data indicate that basicity is one of the controlling features of the nucleophile. Polarisability is not important for displacement at phosphorus to judge from the low reactivity of thiophenoxide ion in the nucleophilicity series toward the phosphinochloridates, $R_2P(O)Cl$, found by Dostrovsky and Halmann.[73]

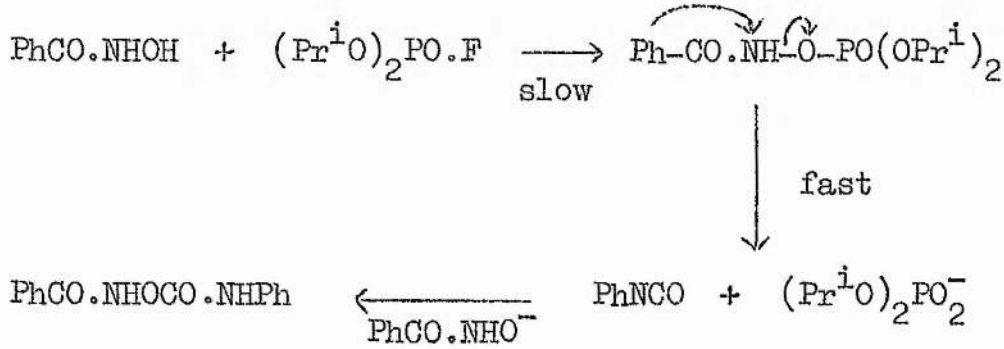
The so-called α-effect is a feature of some nucleophiles with enhanced reactivity towards phosphorus, whereby the presence of an unshared pair of electrons α to the attacking atom increases the rate of reaction beyond that expected from the pK_a of the conjugate acid.[74] The reasons for the enhanced reactivity are not well understood and a number of empirical explanations have been proposed by Edwards and his co-workers.[75]

A charge effect has been described for nucleophilic displacements at phosphorus. The reactivity of isopropyl methylphosphonofluoridate (sarin) with various anions of hydroxybenzenes has shown that the incorporation of a cationic site in the benzene nucleus increased the reactivity relative to the basic strength.[76]

Nucleophiles showing the α-effect have been described[77] to show a catalytic effect on the rate of hydrolysis of the phosphorus

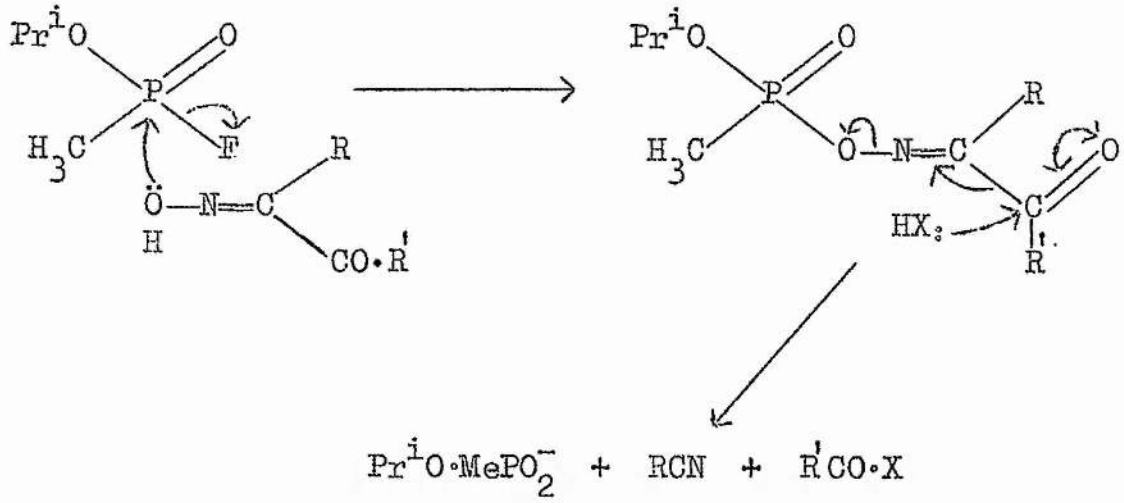
compound. While they certainly increase the rate of hydrolysis, they are not true catalysts as they are often poor leaving groups, and decomposition of the intermediate leads to products which are more complicated than would be expected from a second displacement at phosphorus.

The hydrolysis of diisopropyl phosphorofluoridate at pH 6 has been shown to be accelerated[77] in the presence of the α-nucleophiles, hydroxamic acids. These are poor leaving groups, so that a second displacement by solvent water does not occur. Samuel and Silver[78] confirmed that the reaction involved rate-determining attack by the hydroxamic acid, followed by a Lossen rearrangement to yield diisopropyl phosphate and a carbamate, by their observation that no incorporation of ^{18}O occurred during the reaction in enriched water. The formation of the carbamate thus follows:-



Green and Saville[79] demonstrated that oximes are effective nucleophiles towards phosphorus. Hydrolysis of sarin by the oxime,

$R'CO.C(R)=NOH$, led to isopropyl hydrogen methylphosphonate, fluoride ion, a nitrile, and a carboxylic acid. They postulated the mechanism of breakdown as following:-



$$Pr^iO{\cdot}MePO_2^- + RCN + R'CO{\cdot}X$$

In support of their scheme they found that added aniline became acylated by the intermediate phosphonylated hydroxamic acid.

Similar instability of phosphylated pyridine aldoximes has been reported by Steinberg and Solomon[80] and Van Houidonk[81] et al. In both cases, breakdown occurred to yield the corresponding cyanopyridine and a phosphylate acid anion. In the presence of powerful nucleophiles, normal hydrolysis occurred to yield the aldoxime, rather than elimination.[80]

Hydrolysis Accompanied by Alkyl-Oxygen Fission

The moiety $\rangle PO_2^-$ is a good leaving group because the lone pair of electrons contributing to the negative charge can overlap

with the d orbitals of phosphorus to form a resonance stabilised ion. Consequently, a change from bimolecular reaction at carbon to unimolecular fission of the carbon-oxygen bond should be observed, when the alkyl ester moiety is capable of forming a stable carbonium ion in a solvent of sufficient ionising power.

Gerrard et al. demonstrated[82] this change-over in mechanism in the case of optically active tri-2-octyl phosphate. Dry hydrogen bromide converted this compound, with inversion of configuration, into the optically active 2-octyl bromide by bimolecular attack on carbon. In hydrobromic acid, racemic 2-octanol was obtained, which indicated a unimolecular pathway involving a carbonium ion.

The variation in the rate of acid hydrolysis for a series of dialkyl methylphosphonate esters, $(RO)_2P(O)Me$, has been reported by Hudson and Keay.[61] In 1N benzenesulphonic acid solution, the diisopropyl ester hydrolysed 25 times as rapidly as the diethyl ester which hydrolysed at the same rate as the dineopentyl ester. Thus, these values suggest that carbon-oxygen fission occurs in the diisopropyl and dineopentyl cases where the formation of carbonium ions is favoured by the secondary alkyl structure and the incipient rearrangement to a secondary carbonium ion, respectively. Support for the existence of the neopentyl carbonium ion comes from the

isolation of 2-methylbut-2-ene from the hydrolysis mixture under conditions where neopentyl alcohol is not dehydrated.

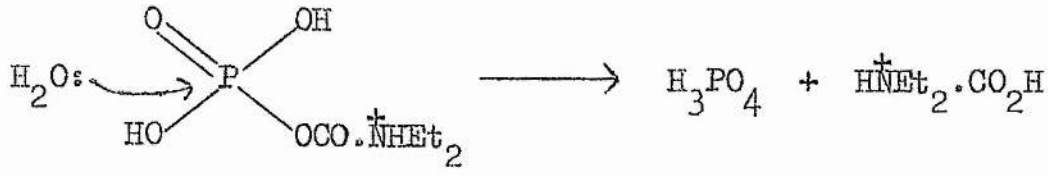
Further evidence of the unimolecular fission in secondary alkyl esters has been provided by Keay,[83] who showed that the rate of loss of optical activity was exactly equal to the rate of formation of ethyl hydrogen methylphosphonate in the acid hydrolysis of optically active ethyl 2-octyl methylphosphonate.

Catalysis of Hydrolysis of Phosphorus Esters

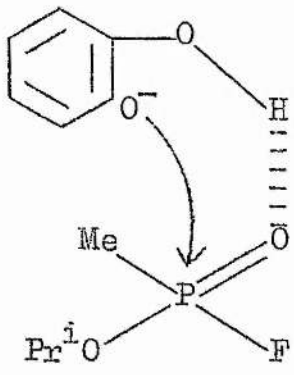
Specific acid catalysis has been demonstrated for a few substrates by the kinetic isotope effect. Deuterium oxide has a smaller autopyrolysis constant (x 5) than water and is thus believed to be less basic. The substrate then competes more effectively with the solvent for the deuteron in deuterium oxide, than the proton in protium oxide (water). Since the concentration of the substrate is greater, the rate of reaction should be higher in deuterium oxide than in protium oxide, provided that the second step does not show a kinetic isotope effect.[84]

A kinetic investigation by Lapidot and his co-workers[85] of the hydrolysis of N,N-dimethyl carbamyl phosphate in strongly acid solution revealed that the rate was a function of the stoicheiometric concentration of acid. These workers observed a solvent

isotope effect of k_D/k_H = 1·4 and they interpreted this, together with the occurrence of phosphorus–oxygen fission, as indicating a bimolecular attack of water on the protonated substrate thus:



Intramolecular general acid catalysis has been demonstrated with o-substituted phenols.[86] Catechol monoanions (25) reacted more rapidly than phenoxide ions, as also did the ammonium salt of o-hydroxyphenylmethyl dimethyl amine (26), with sarin. It is not known with certainty whether the catalysis is operative at the phosphoryl group or at the fluoride leaving group.[86]



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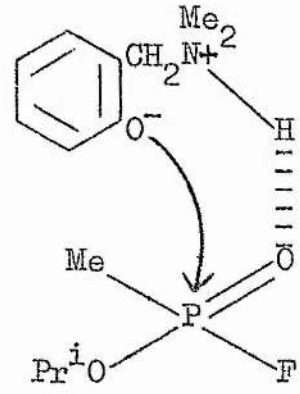
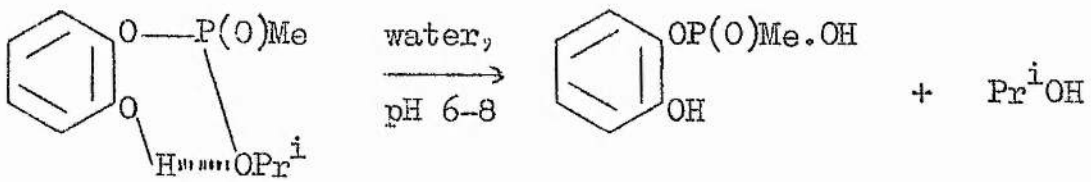


(26)

A measure of the greater leaving ability of the fluoride ion

in those cases is afforded by the Brønsted β coefficient. Its value is an estimate of the degree of bond formation with the nucleophile in the transition state. The value of β for aryloxide attack on sarin has been given as 0.59, whereas for catechol monoanion the value rose to 0.90. The increase represents the greater ease of departure of the fluoride ion, possibly as a result of hydrogen bonding by the phenolic hydrogen.[87]

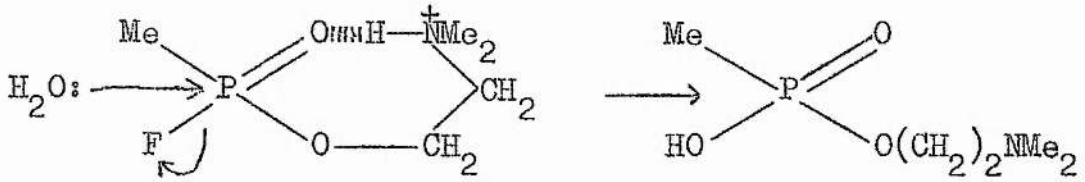
Dealkylation of isopropyl 3-nitro-2-hydroxyphenyl methylphosphonate has been shown to occur readily at pH 6-8 under acid catalysis from the neighbouring hydroxyl group thus:



Mlodozeniec[88] obtained a half-life of 30 minutes at 30° for this dealkylation. Again, whether the effect of the hydroxyl group involves anchimeric assistance in the solvolysis of the neighbouring isopropyl group or just a stabilising effect of hydrogen bonding between the vicinal hydroxide and the phosphoryl oxygen is not known. Only at high pH, 10-13, was there loss of 3-nitrocatechol from the phosphorus centre.

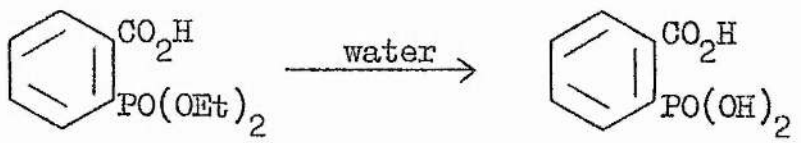
N,N-Dimethyl aminoethoxy methylphosphonofluoridate[89] is rapidly hydrolysed in aqueous solution at pH 6, with a half-life of

7 minutes at room temperature, the rate of reaction at pH 8 being too fast to measure. Protonation of the amino function in solution could lead to acid catalysis in this case. The alternative reaction, at intermediate pH, of nucleophilic attack by

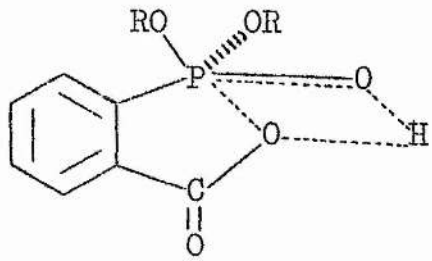


nitrogen followed by acid catalysed hydrolysis of the phosphoramidate formed, does not seem likely since it has been shown that the solid obtained from the self-reaction of the fluoridate, the structure of which has been confirmed to be that of a cyclic salt,[90] was only hydrolysed at pH 1.

General acid catalysis by a neighbouring carboxyl group has been reported by Griffin and his co-workers.[91] Thus, the rapid hydrolysis of diethyl o-carboxyphenylphosphonate has been observed, but no enhanced reactivity for the p-isomer, or the o-ethyl carboxylate ester. The anchimeric assistance due to the o-carboxyl group was estimated at 8×10^7.

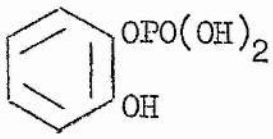


In a recent study of this reaction, Blackburn and Brown have postulated a concerted four-centre transition state as being in accord with their observations on the intermediates in the hydrolysis.



They were able to detect the mono-ester in an interrupted hydrolysis in deuterated solvents by n.m.r. spectroscopy and a hydroxamic acid from the slow hydrolysis of the diester in 4M hydroxylamine. The formation of the latter was taken as evidence of the existence of an anhydride intermediate, an independent synthesis of which showed it to react rapidly under the reaction conditions. The formation of hydroxamic acids is a known characteristic of acyl phosphates and no such formation occurred with the diester, monoester, or final hydrolysis product. These workers believe the hydrolysis thus proceeds through successive anhydride intermediates with alternate ring closing and opening processes.

A further example of acid catalysis has been provided by Bender and Lawlor[93] in the hydrolysis of salicyl phosphate (26). The rate of hydrolysis was very much greater than that of simple



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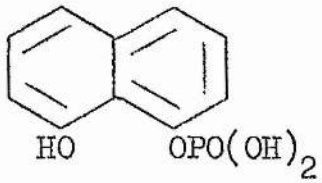
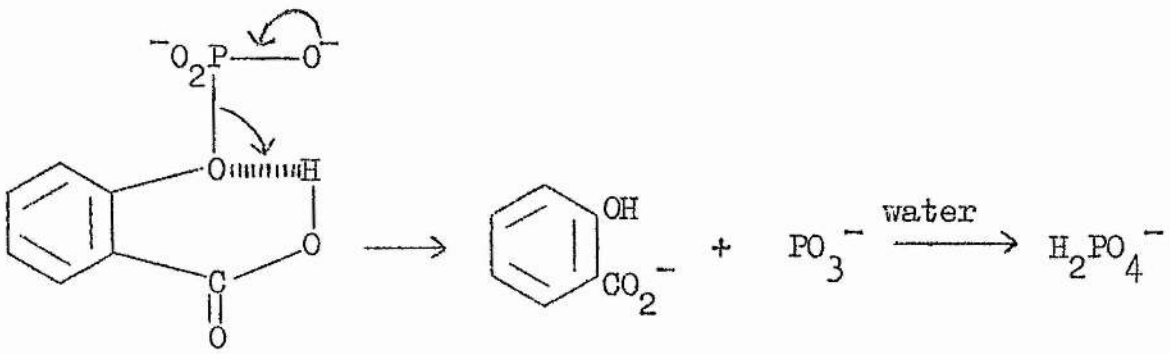


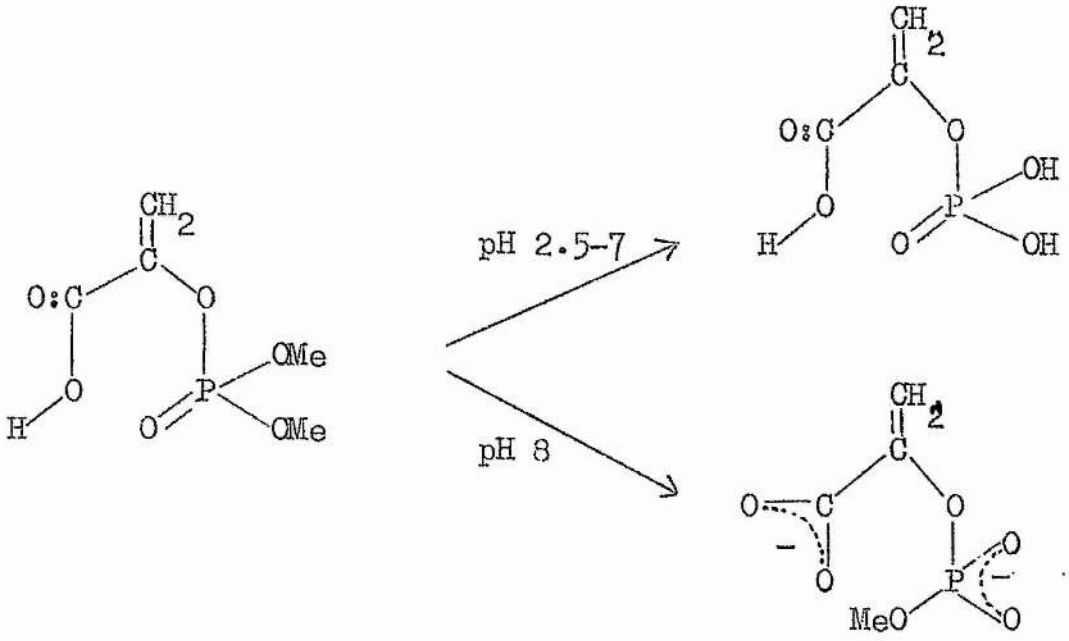
(27)

aromatic esters and greater than that of the p-isomer. The rate profile has a maximum at pH 5, which corresponds to the dianionic species. Intramolecular catalysis has been postulated for the rate acceleration, with the formation of metaphosphate ion, which is rapidly attacked by water. Nucleophilic catalysis by the



carboxylate group was shown to be absent. Such catalysis was definitely absent in the analogous naphthalene derivative (27), which was also rapidly hydrolysed. In this latter case, nucleophilic attack by the neighbouring carboxylate group would simply regenerate the starting material. Again, the mechanism probably involves donation of a proton to the leaving oxygen atom in the hydrolysis, followed by elimination of metaphosphate ion.

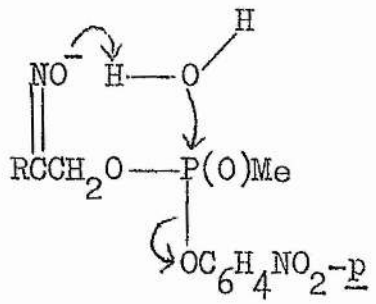
A related example of neighbouring group acceleration has been reported by Clark and Kirby[94] for the hydrolysis of the esters of phosphoenol pyruvic acid. Rapid hydrolysis to phosphoenol pyruvate occurred under mildly acid conditions, while in bicarbonate buffer at pH 8, the monomethyl ester was formed quantatively.



It is again likely that internal protonation of the leaving oxygen atom by the carboxyl group, followed by attack of nucleophilic water, is responsible for this rapid hydrolysis of the monomethyl ester.

Catalysis involving a neighbouring oxime group has been reported by Steinberg and his co-workers,[95] who showed an accelerated hydrolysis of p-nitrophenyl phenacyl methylphosphonate oxime

(28). The hydrolysis was first-order in hydroxide ion and in substrate, and the production of p-nitrophenol was concurrent with that of the acid hydrolysis product. The reaction was studied



(28)

between the region pH 3.49 and 4.90 (half-life 1.34 minutes) and gave a solvent isotope effect k_D/k_H of 1.24.

These workers suggested that a water-mediated attack occurred involving the oximate anion (28).

They discounted direct attack on the phosphorus centre by the oximate anion, since the rate of formation of the acid and p-nitrophenol were identical. Direct attack by hydroxide ion on phosphorus, facilitated by hydrogen bonding from the oxime, was rejected because of the lack of increase in reaction rate with more nucleophilic anions.

Berlin and his co-workers[96] have described the preparation

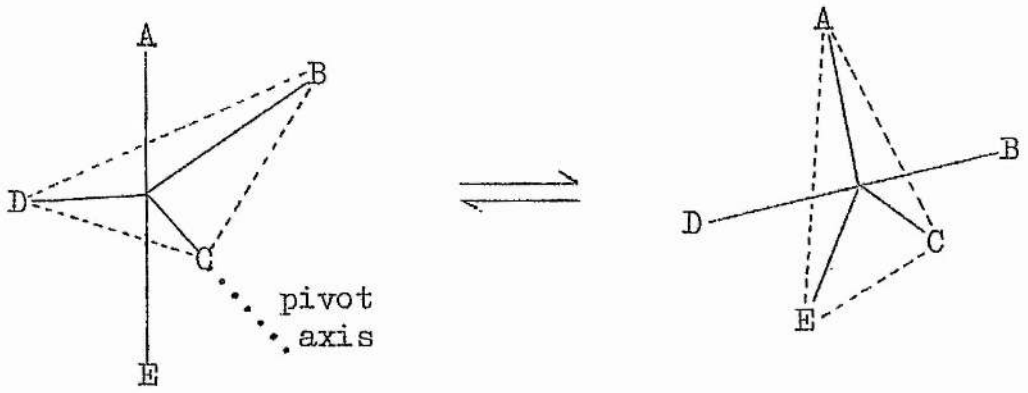
of the oximes of diethyl aroylphosphonates in an alcoholic solvent with hydroxylamine and a slight excess of pyridine. Transesterification was observed at room temperature over a three-day period. This is to be compared with practical preparations[97] by transesterification, which require reaction times of 6 days at 130° in sealed tubes. Some anchimeric assistance is thus available for the solvolysis of diethyl aroylphosphonate oximes.

Pseudo-Rotation in the Hydrolyses of Phosphorus Compounds

Westheimer[98] has further developed the concept of pseudo-rotation, which was originally advanced as an explanation of the results obtained from physical measurements on fluorophosphoranes, as a means of correlating and predicting the behaviour of cyclic phosphorus compounds.

Pseudo-rotation is an intramolecular exchange for trigonal bipyramidal substituents of the axial and equatorial positions. The transformation takes place in such a way that the molecule appears to be rotated by 90° about one of the interatomic bonds (called the pivot). The process is illustrated for the pseudo-rotation of the five-coordinate phosphorus compound PABCDE.

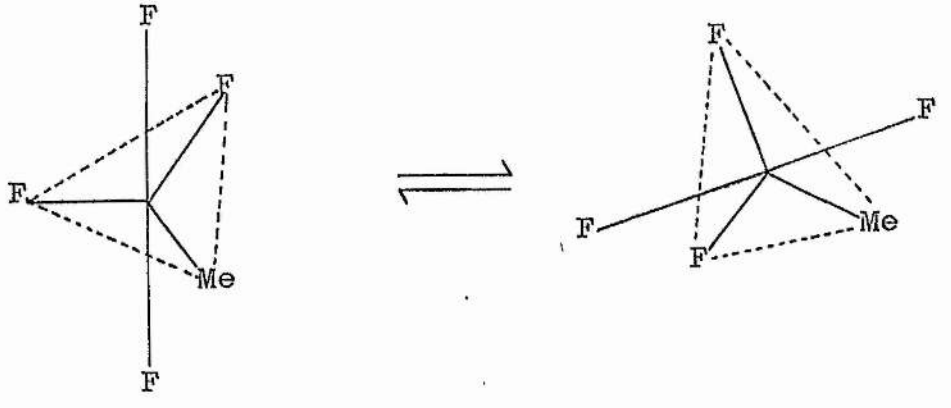
The phosphorus atom is understood to occupy the centre of the trigonal bipyramid, with the equatorial substituents B, C and D



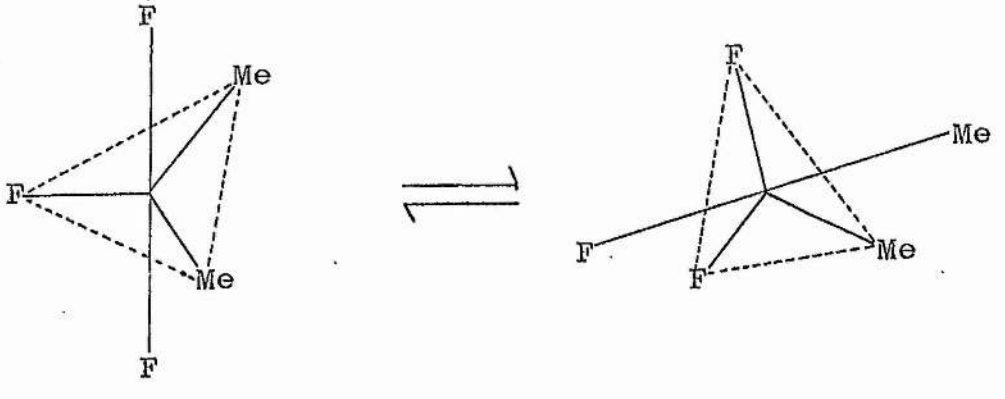
linked in a triangle to indicate the equatorial plane. After the pseudo-rotation, two of the equatorial substituents have exchanged positions to become apical substituents, while the third, C, has retained its equatorial position by lying on the pivot axis.

Pseudo-rotation will first be discussed in relation to stable pentacoordinate phosphorus compounds, and then its occurrence in reactions where the transition state in a normal bimolecular displacement at phosphorus has become an intermediate with a finite lifetime.

The fluorine n.m.r. spectra of the alkylfluorophosphoranes, $(CH_3)_nPF_{5-n}$, were found to fall into two categories, those that had equivalent fluorine atoms and those that had more than one kind of fluorine signal. Muetterties and Schmutzler[99] rationalised these facts on the basis that the structures were trigonal bipyramids (since confirmed by electron diffraction experiments)[100] with the more electronegative fluorine atoms in apical positions.



Allowed; equivalent fluorine p.m.r. signals



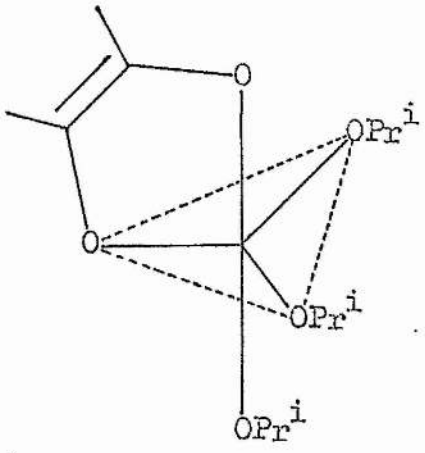
Not allowed;differing fluorine p.m.r.signals in ratio 2:I. Equivalent proton spectra.

Pseudo-rotation would be allowed for PF_5 and CH_3PF_4, where an alkyl group would not be forced into an apical position giving rise to a structure of higher energy. Equilibration of the fluorine atoms would result in only one n.m.r. signal Pseudo-rotation would not be allowed for di- or trialkylphosphoranes where such a rotation would force an alkyl group into an apical position. For these latter examples, different fluorine n.m.r. signals were observed, corresponding to apical and equatorial atoms. Equivalent proton spectra were observed. The fact that pseudo-rotation is a function of the polarity of the substituents, and not of the size, comes from the n.m.r. spectrum of H_2PF_3,[101] where at low temperatures separate signals were again recorded for apical and equatorial fluorine atoms. In a further analogy with methyltetrafluorophosphorane, the hydrogen atom of hydrogentetrafluorophosphorane, HPF_4, lies equatorially.[102]

Many alkyloxyphosphoranes have been synthesised[103] and n.m.r. and crystallographic studies reported for oxyphosphoranes containing a five-membered ring.[104] The so-called 'preference rules' for such structures have been stated[105] to be, (a) that the more polar atoms occupy apical positions and the less polar atoms occupy equatorial positions and (b) that five-membered rings are best placed so as to span one equatorial and one apical position. It is also known that

pentaoxyphosphoranes having saturated and unsaturated rings are more stable than those lacking the ring.[106]

An X-ray crystallographic determination[107] of a phosphorane containing a five-membered ring (31) confirmed that its position lay in an apical-equatorial configuration with an OPO angle close to 90°.



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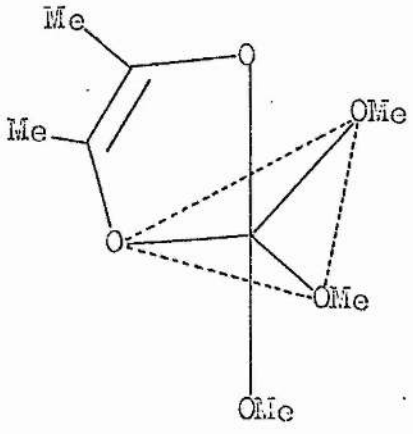
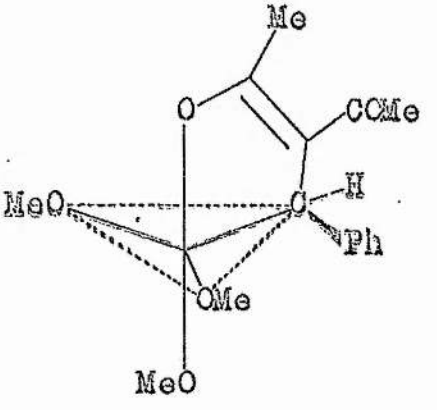


(32)

The temperature dependence of the n.m.r. spectrum for some cyclic oxyphosphoranes has provided further confirmation of the preferred apical-equatorial conformation. The methoxyl p.m.r. signals of the phosphorane (32) are all equivalent, even at -100°. Pseudo-rotation is allowed, in a complete analogy to PF_5.[108]

Gorenstein and Westheimer[109] have examined the n.m.r. spectrum temperature dependence of the cyclic phosphorane (33). At room temperature, they found equivalent methoxyl signals due to ready pseudo-rotation into the two other forms (34) and (35). However, at low temperatures, two different methoxyl signals, apical and



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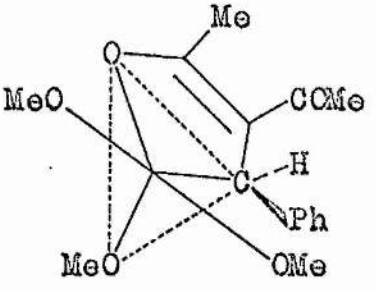

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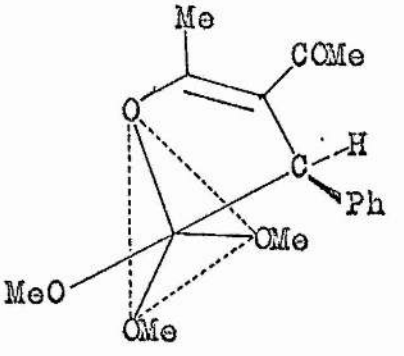


(34)

equatorial, were observed of area 1:2 respectively. This was taken to be consistent with the molecule being locked into a trigonal bipyramidal configuration with the more electro-negative oxygen atom of the ring lying apically. At room temperatures, the thermal motions were sufficient to overcome the barriers to placing a carbon

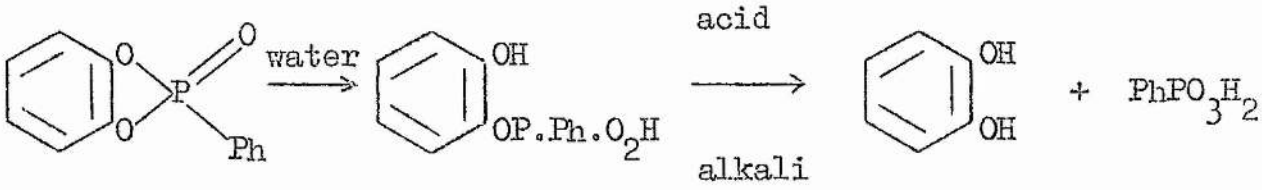
atom in the apical position (34) or requiring the plane of the ring to lie diequatorially with a ring angle at phosphorus of 120° (35). This equatorial positioning of the ring has been shown to be of higher strain energy [53,110] than the apical equatorial configuration and therefore can be expected to be inhibited.

It is seen that the less electronegative atom, oxygen (compared with fluorine), obeys less rigidly the rule that it should occupy an apical position in the trigonal bipyramid. In the case of fluorine, a single conformation was held at all temperatures for $(CH_3)_2PF_3$, whereas for oxygen, pseudo-rotation which places oxygen equatorially and carbon apically would seem to be allowed if the thermal energy of the molecule is sufficient to overcome the barrier to pseudo-rotation.[98]

Hydrolysis of Cyclic Phosphorus Esters

The hydrolysis of five-membered cyclic esters proceeds 10^6–10^8 times more rapidly than those of their acyclic analogues.[98] The hydrolysis is generally acid or base catalysed, but a measurable rate is often obtained even in water. Thus, the cyclic phosphonate (36) is hydrolysed rapidly to form the mono-ester and spontaneously in acid or alkali to form the free phenylphosphonic acid.[111]

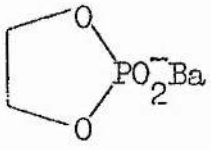
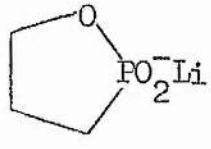
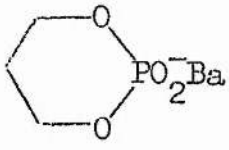
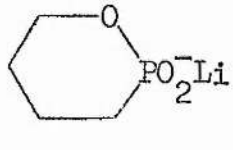
Acceleration of the hydrolysis in cyclic phosphorus esters is



(36)

only observed in five-membered rings. The six-membered rings react more nearly at the rate of the acyclic analogue (Table 14).

TABLE 14: Ring-Opening Hydrolyses of some Phosphorus Esters

	Phosphates[114]	k_{rel}	Phostonates[115]	k_{rel} acid	k_{rel} alkali
Five-membered ring		10^8		5×10^4	6×10^5
Six-membered ring		3		5	24
Acyclic analogue	$(MeO)_2PO_2^-$	1	$EtO\cdot EtPO_2^-$	1	1

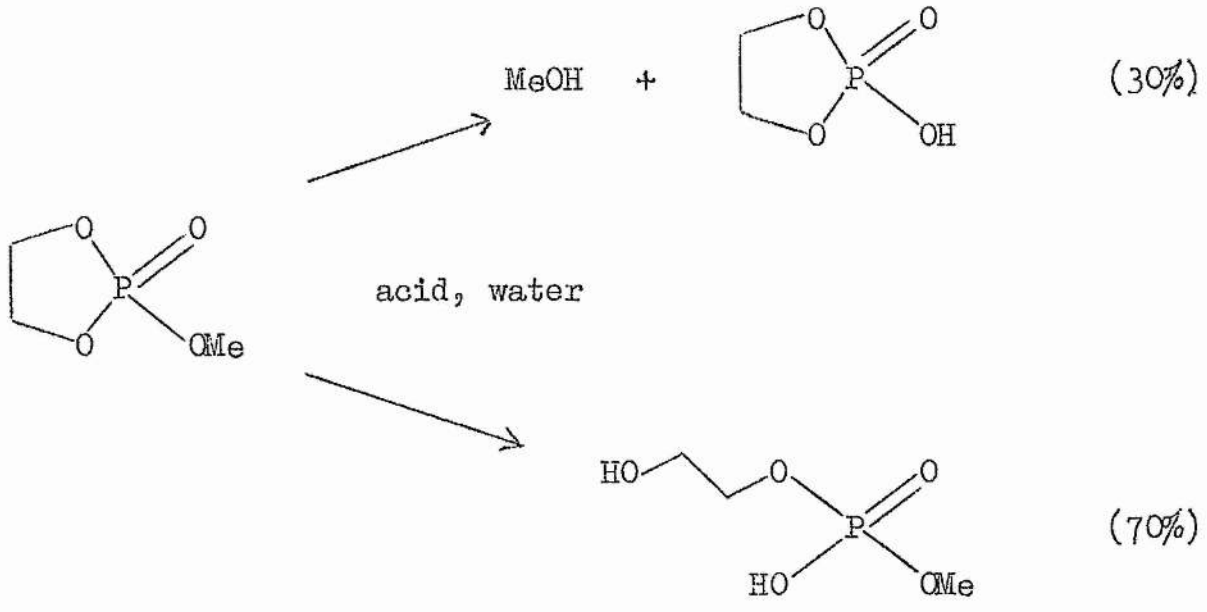
Aksnes and Bergesen have measured the alkaline rates of hydrolysis of cyclic phosphates and phosphonates and have observed that the phostonate containing the phosphorus atom in a seven-membered ring

was more stable by a factor of 25 than the six-membered ring. (A phostonate is the name used by Westheimer[115] to describe a cyclic phosphonate with one oxygen atom in the ring.) This extra stability of the seven-membered ring is not limited to phosphonate esters since Khorana and his co-workers[113] have also observed the greater stability of the seven-membered cyclic phosphate ester compared with the corresponding six-membered ester. These workers have also demonstrated that the same order of stability is found in the five-, six- and seven-membered cyclic phosphate esters under acidic hydrolysis conditions.

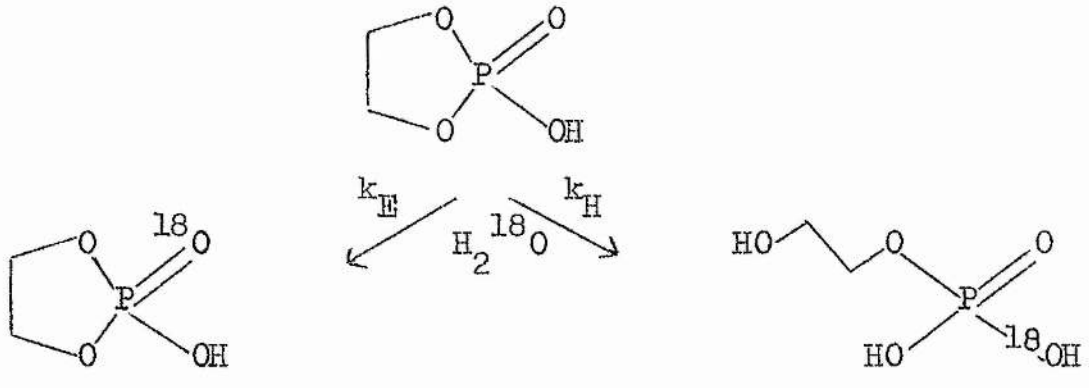
Ring opening reactions for three- and four-membered rings have not yet been studied.

The position of hydrolysis also varies in these cyclic esters. 2-oxo-2-methoxy-1,2-oxaphospholan (Westheimer calls this compound "methyl propylphostonate") was hydrolysed in both acid and alkaline solution with almost complete ($>99.8\%$) ring opening.[115] The hydrolysis of 2-oxo-2-methoxy-1,3,2-dioxaphospholan ("methyl ethylene phosphate") was accompanied by exclusive phosphorus-oxygen fission in alkaline and acid solutions. In acid solution the compound hydrolysed with some retention of the ring (p. 96).

Rapid exchange of ^{18}O from enriched water accompanied the hydrolysis of 2-oxo-2-hydroxy-1,3,2-dioxaphospholan in acid solution



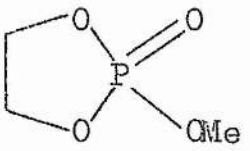
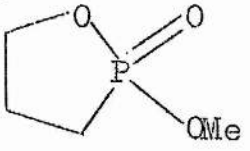
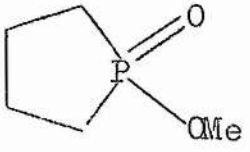
to become incorporated into the starting material. The ratio of k_H/k_E was about five, and since the hydrolysis was about 10^8 times faster than that of hydrogen dimethyl phosphate, it follows that the oxygen exchange was about 2×10^7 times faster than the hydrolysis of hydrogen dimethyl phosphate.



Cyclic phosphinates are only slightly accelerated in their rates of hydrolysis, which are comparable with their acyclic analogues.[112,116] Bergesen and Aksnes[112] demonstrated carbon-oxygen fission for the acid hydrolysis of cyclic phosphinates. The rates of hydrolysis of 2-oxo-2-ethoxy phospholan and ethyl diethylphosphinate were similar and no incorporation of ^{18}O label was found in the cyclic ester, after it had been boiled in acidified acetonitrile containing enriched water.

The rates of hydrolysis of the cyclic esters are compared (Table 15).

TABLE 15: Rates of Hydrolysis of Cyclic Phosphorus Esters

	Relative rate compared with acyclic analogue	
	Exocyclic	Ring opening
117 	10^6	10^8
115 	1	10^6
116 	4	-

Westheimer and his associates rationalised these experimental results by invoking pseudo-rotation of a five-coordinate intermediate, subject to four conditions:-[105]

(a) It is energetically unfavourable for a carbon atom to occupy an apical position.

(b) It is energetically favourable for a five-membered ring to occupy an apical-equatorial configuration.

(c) Pseudo-rotation only occurs if the above two conditions are fulfilled.

(d) Groups enter and leave from apical positions.

The first two conditions are suggested by the behaviour of the oxyphosphoranes already discussed and the fourth from the principle of microscopic reversibility. Parallel rate increases[53] for ^{18}O exchange with the solvent and for ester hydrolysis with 2-oxo-2-hydroxy-1,3,2-dioxaphospholan show that the water leaving group (for exchange) and the ester leaving group (for hydrolysis) must occupy equivalent positions.

The pentacoordinate intermediate formed in the acid hydrolysis of 2-oxo-2-methoxy-1,3,2-dioxaphospholan undergoes pseudo-rotation to fulfil the experimental demands made on it in the product analysis. Rapid hydrolysis exo to, or in, the ring can occur without any of the constraints that carbon atoms cannot be placed

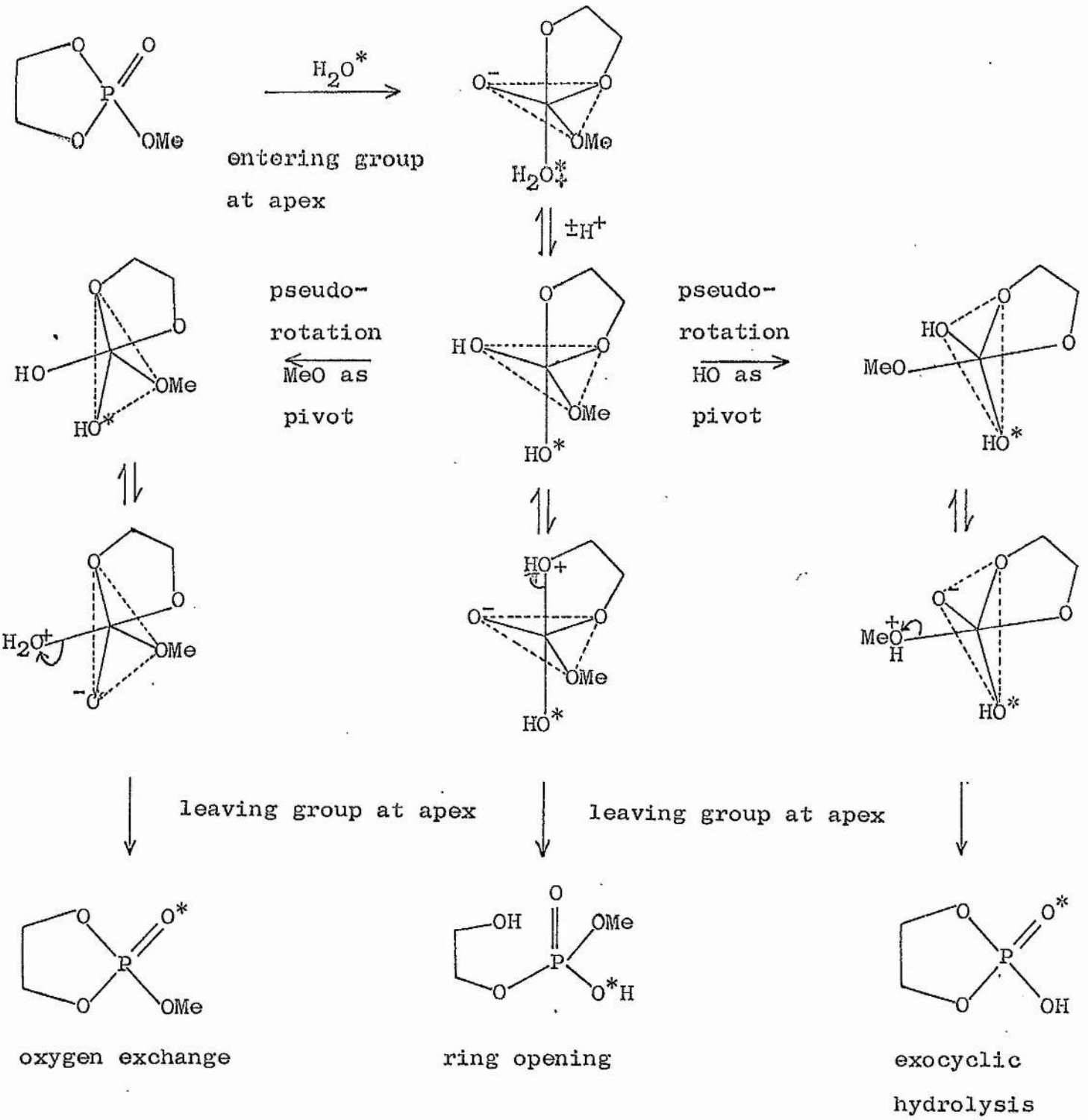
apically or the ring diequatorially being violated (Scheme 8, page 100).

The intermediate in the hydrolysis of 2-oxo-2-methoxy -1,2-oxaphospholan cannot readily undergo pseudo-rotation to allow the methoxyl group to leave from an apical position, without the ring being in a diequatorial configuration or a carbon atom being forced into an apical position. The only permissible reaction is of rapid ring hydrolysis, which is in accord with the observed $> 99.8\%$ ring opening and $< 0.2\%$ exocyclic hydrolysis (Scheme 9, page 101).

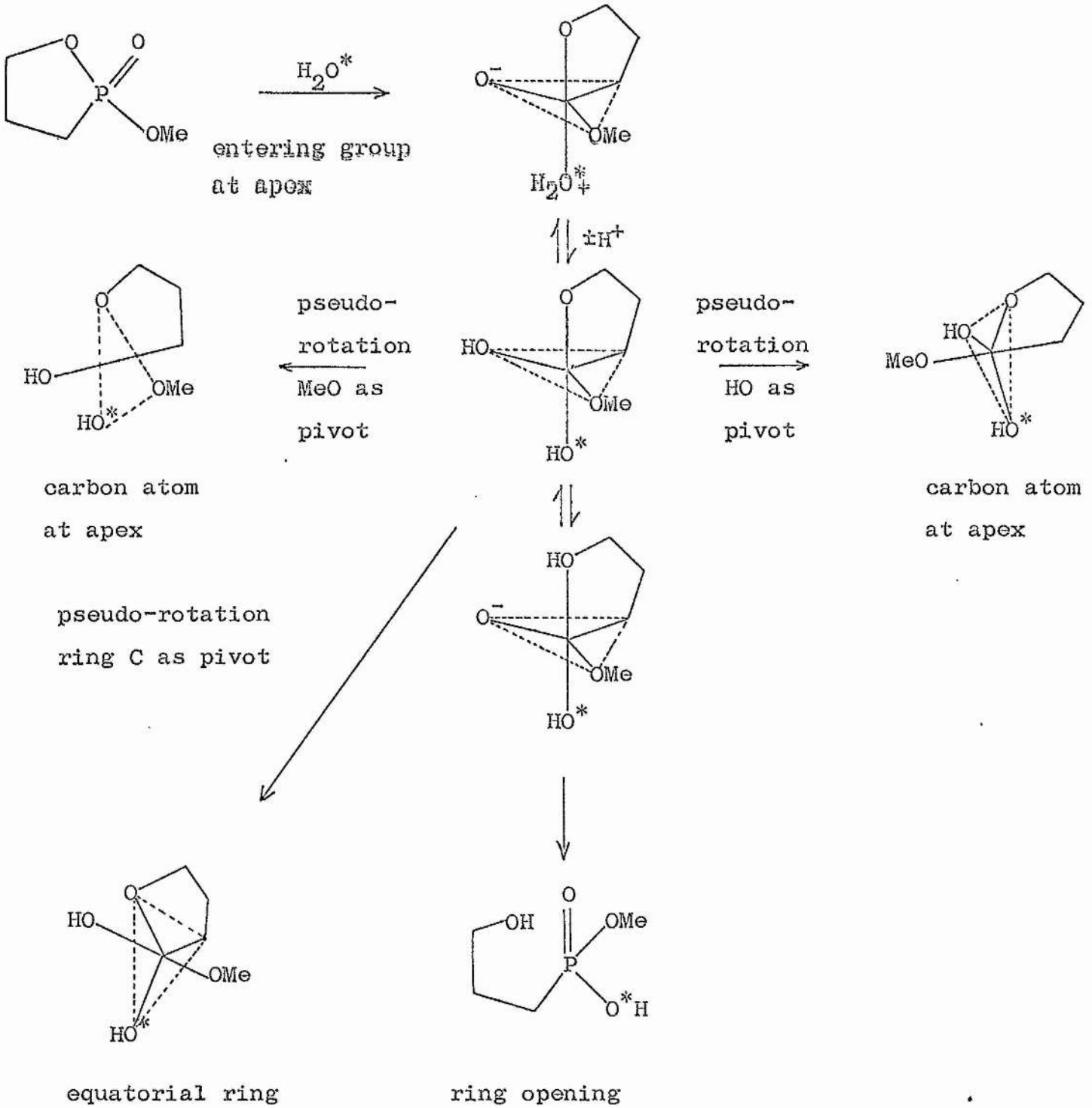
The rate of reaction of cyclic phosphinate esters is expected to be low, since there is no way in which to form a trigonal bipyramidal intermediate of low energy, whereby the ester moiety could leave from an apical position. The ring angle must either be expanded to a 120° diequatorial configuration or an alkyl group be placed in an apical position. Although neither of these intermediates is forbidden, the formation of either will necessarily be accompanied by an increase in energy and a consequent drop in rate.

Corroboration of the features of Westheimer's hypothesis comes from molecular orbital calculations on cyclic and acyclic esters made by Boyd.[118] Ring-strain in the five-membered ring of 2-oxo-2-methoxy-1,3,2-dioxaphospholan results in a lowered

Scheme 8. Pseudo-Rotation for the Hydrolysis of 2-Oxo-2-Methoxy -1,3,2-Dioxaphospholan ("Methyl Ethylene Phosphate").

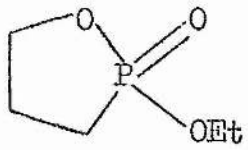


Scheme 9. Pseudo-Rotation for the Hydrolysis of 2-Oxo-2-Methoxy -1,2-Oxaphospholan ("Methyl Propylphostonate").



occupation of the phosphorus 3d orbitals. The resultant de-shielding of the phosphorus nucleus then accounts for the high rate of nucleophilic attack. The lowest calculated activation energies were those of a system in which the nucleophile approaches the ester on the backside of one of the ring phosphorus-oxygen bonds. This bond lengthens to become an apical bond in a trigonal bipyramidal intermediate. Pseudo-rotation occurs when the phosphoryl group remains in an equatorial position, i.e. serves as the pivot bond. The apical oxygen bonds are the most readily protonated and after the leaving group has departed from the phosphorus atom, the local geometry relaxes towards tetrahedral.

It is not necessary to postulate five-coordinate intermediates in the alkaline hydrolyses of the esters. The lack of exchange of oxygen, ^{18}O, under alkaline conditions for 2-oxo-2-methoxy -1,3,2-dioxaphospholan is probably due to the lower stability of a negatively charged intermediate, which gives rise to direct bimolecular displacement via a transition state and not a stable intermediate.[98, 112]



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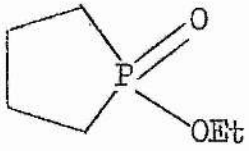


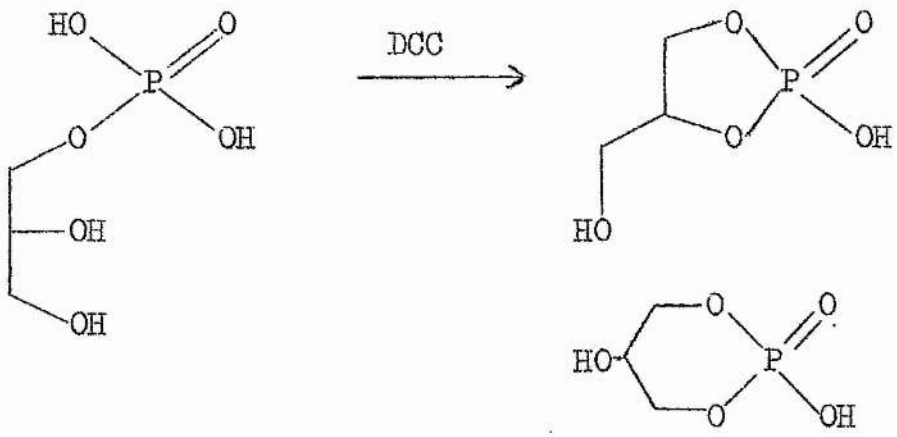
(38)

Aksnes and Bergesen have shown that the greater rate of the hydrolysis of the oxaphospholan (37) compared with the phospholan (38) arises from a more favourable entropy of activation. The entropy difference corresponds to a rate factor of about 10^4, while the difference in the activation energies corresponds to a rate factor of 50. They ascribe the more favourable entropy to solvation and steric effects.[112]

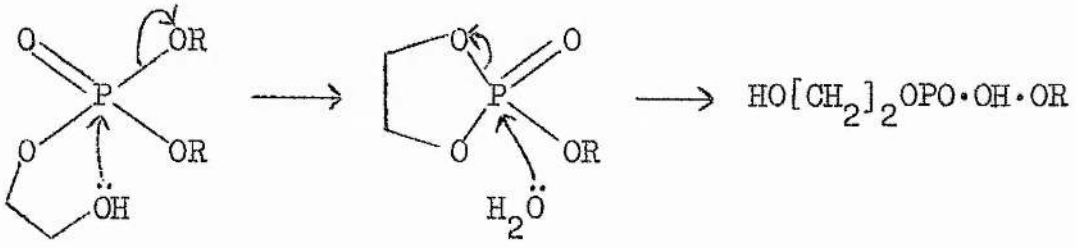
Kugel and Halmann[119] considered that the high negative value of the activation entropy in the alkaline hydrolysis of glycero -1,2-cyclic phosphate, together with the lack of reaction at pH 3-10, indicated a transition state which lay in the bond-forming stage. The implication of this, then, is that the ring is substantially intact during the transition state.

The Special Reactivity of Five-membered Rings

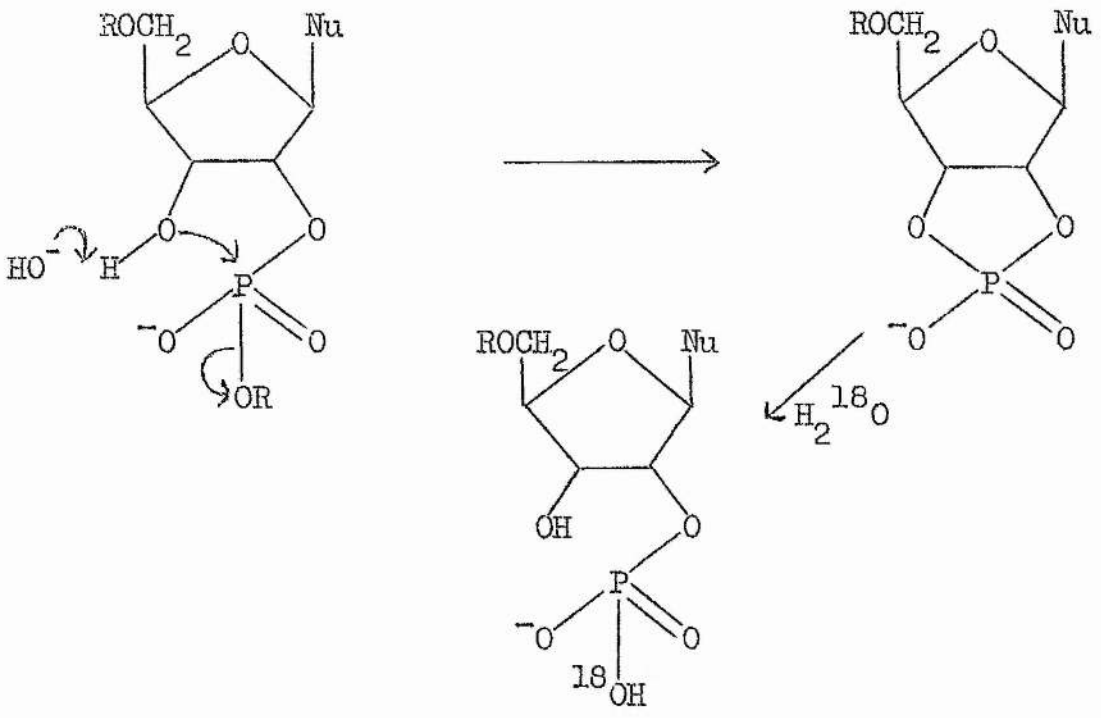
Generally, five-membered rings are formed more readily than six-membered rings, although the latter are more thermodynamically stable. For example, the reaction of glycerol phosphate in the presence of a condensing agent, dicyclohexylcarbodiimide (DCC), yields only the five-membered ring ester.[120]



In many cases, the formation of the ring is immediately followed by ring opening. Phosphate triesters with neighbouring hydroxyl groups lose one esterifying group at room temperature in aqueous solution at neutral pH.[121]



The alkaline hydrolysis of ribonucleic acid[122] also follows this pathway thus:



The Origin of the Reactivity of Five-membered Rings

Westheimer and his co-workers have proposed that the strain inherent in five-membered rings facilitates the formation of a trigonal bipyramidal intermediate.[116] The nature of this strain has been attributed either to the effects of angle strain in the ring or to the 2p-3d π character of the ring phosphorus-oxygen bonds.

A calculated value of the strain energy of 2-oxo-2-methoxy -1,3,2-dioxaphospholan was obtained by Westheimer,[110] who minimised the energy with respect to all possible variations

in the bond angles. The calculated OPO angle obtained was later shown to be in excellent agreement with the experimental value from the X-ray crystallographic structure determination[123] of the cyclic phosphate ester.

The magnitude of the relief of strain in forming the transition state depended on the absolute values of the bond force-constants chosen, but was determined to lie in the range 3-6 Kcals./mole. The value of the strain energy has been experimentally estimated by comparison of the heats of hydrolysis of 2-oxo-2-methoxy-1,3,2-dioxaphospholan and trimethyl phosphate or dimethyl hydroxyethyl phosphate, where the difference is about 5-6 Kcals./mole.[124]

The rate of alkaline hydrolysis of 2-oxo-2-methoxy-1,3, 2-dioxaphospholan exceeds that of trimethyl phosphate by a factor of about 10^6, which corresponds to a free energy of activation difference of about 8·5 Kcals./mole. The difference in the energy of activation for these two hydrolyses is comparable (7·5 Kcals./mole), but both figures exceed the thermo-chemical difference in energy of 5-6 Kcals./mole, which is attributed to ring strain. The latter then provides most, but not all, of the explanation for the rapid reaction of cyclic phosphates.

Kugel and Halmann[119] have questioned Westheimer's

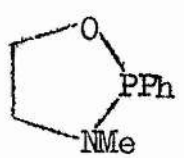
advocacy[98] of ring strain as the driving force for the hydrolyses, and suggested that specific kinetic effects were operative. They found the rate of hydrolysis of glycero-1,2-cyclic phosphate was very slow in the absence of acid or base catalysis. They argued that if relief of ring strain was important, then the hydrolysis should be rapid at all pH. These workers favoured the proposal of Collin[125] that for cyclic phosphorus esters, the reactivity was due to the greater electrophilicity of phosphorus, which was inherent in the reduced net calculated electronic charge. In support of their view, they pointed to the very much lower values of the energies of activation for the cyclic esters compared with the acyclic analogues.

Boyd[118] has confirmed that the phosphorus atom in cyclic triesters is more positive than in comparable acyclic di- and triesters. Newton, Cox, and Bertrand[126] made a similar suggestion that in five-membered cyclic phosphates, one of the phosphorus d orbitals is not used in π-bonding and the availability of such an orbital facilitated both the nucleophilic attack at phosphorus, as well as the formation of the pentaoxyphosphorane, which requires sp^3d hybridisation.

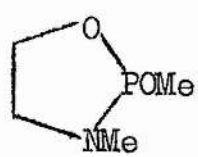
Hudson and Greenhalgh[127] have discussed the possibility

that the greater reactivity of cyclic phosphoramidites towards nucleophiles may arise from the greater accessibility of the phosphorus atom. In cases where the phosphorus atom acts electrophilically, sp^3d hybridisation of the phosphorus atom should lead to a large reduction in the bond angle at phosphorus with a consequent acceleration of the reaction rate. This was confirmed experimentally by the reaction with phenyl isocyanate, where an intramolecular nucleophilic attack on phosphorus occurred more readily for the cyclic ester by a factor of 10^2–10^3.

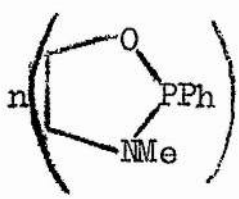
In a later paper, these authors[128] have cast doubt on the validity of ring strain as the driving force, because of the similarity of the heats of hydrolysis for cyclic and acyclic phosphoramidites. Evidence for ring strain in the phosphoramidite (39) was provided by the observations of its greater reactivity (x 140) to the phosphoramidite (40) and its slow, reversible polymerisation at room temperature.



(39)



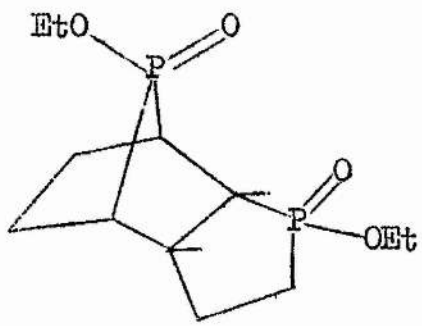
(40)



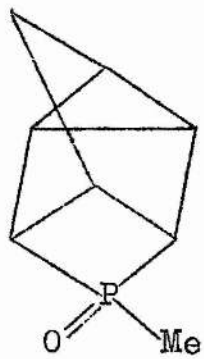
$\xrightarrow[125^\circ]{25^\circ}$ $\left[OCH_2CH_2N(Me)\cdot P\cdot Ph \right]_n$

The origin of the strain was attributed to conjugation between the phosphorus atom and the aromatic ring, which changed the hybridisation at the phosphorus atom.

Ring strain has been thought to be responsible for the enhanced reactions of phosphinates contained as part of a more tightly constrained ring than a five-membered ring. Westheimer and his colleagues[130] reported that a cyclic phosphinate ester held in a bridge-head position (41) was more rapidly hydrolysed than the analogous five-membered ring. The first ester group (41) was hydrolysed more rapidly ($>3 \times 10^{-4}$ $l.mole^{-1}sec.^{-1}$) compared with the second ester moiety (1×10^{-6} $l.mole^{-1}sec.^{-1}$) in the same molecule or 2-oxo-2-ethoxy phospholan (9×10^{-6} $l.mole^{-1}sec.^{-1}$).



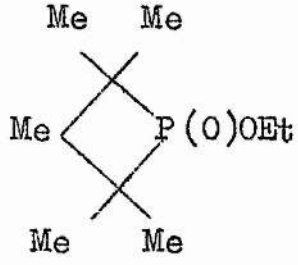
(41)



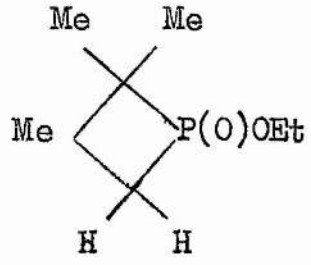
(42)

Rapid oxygen exchange has been reported by Samuel and Silver[51b] in the strained phosphine oxide (42), where by contrast most phosphine oxides exchange sluggishly, if at all. Westheimer[98] has proposed that the increased reactivity of the phosphorus atom held in a bridge-head position results from the greater relief of strain, which exceeds the barrier to placing an alkyl group in the axial position of a pentacoordinate intermediate.

Further acceleration of hydrolysis has been observed by Trippett and Hawes in the phospha-cyclobutan esters (43) and (44). The rate of hydrolysis of the pentamethyl substituted ester was comparable with non-hindered acyclic derivatives and this was thought to represent a balance between acceleration due to ring strain and retardation due to steric hindrance. In support of this, Trippett and Hawes showed that the rate of hydrolysis of the trimethyl substituted ester (44), where the steric hindrance by the flanking methyl groups is reduced, was more rapid by a factor of about 4×10^3.



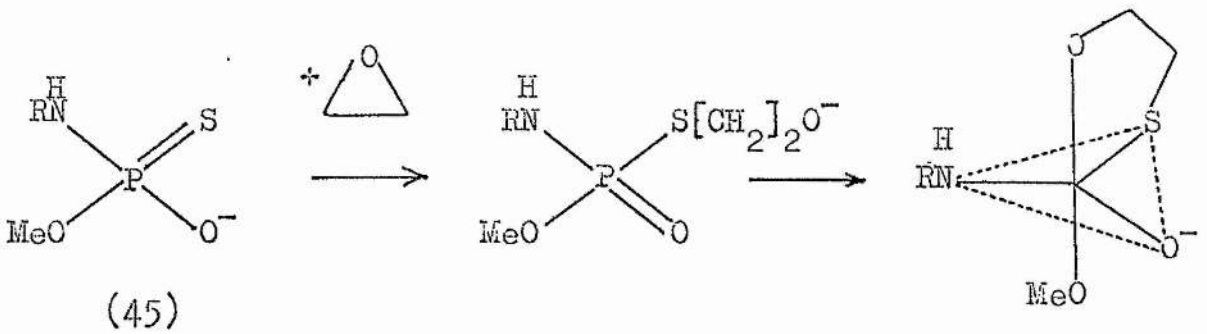
(43)



(44)

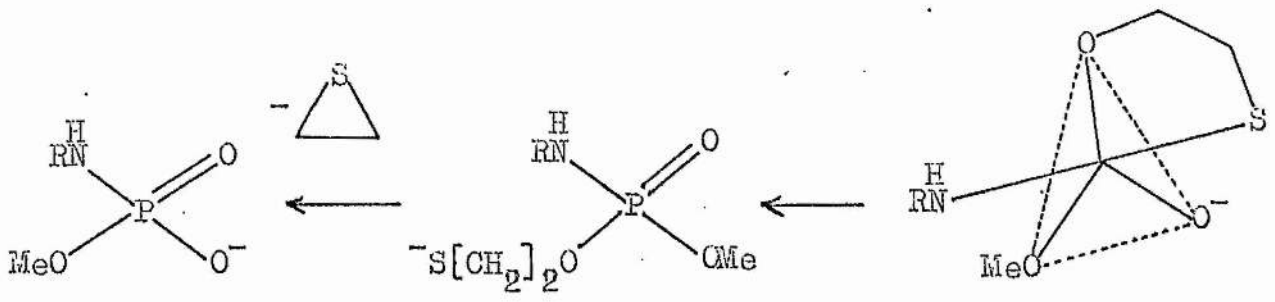
Pseudo-Rotation and Intermediates containing Five-Membered Rings formed by Initial Intramolecular Attack

The existence of five-coordinate intermediates has been postulated in compounds capable of intramolecular attack in order to explain the observed course of the reaction. Hamer[131] demonstrated that the reaction of a phosphorothioate ester (45) with ethylene oxide led to concomitant yields of ethylene sulphide (70%) and sodium methyl N-cyclohexyl phosphoramidate (46) in 85% yield at pH 9-10 in aqueous solution.



(45)

pseudo-rotation



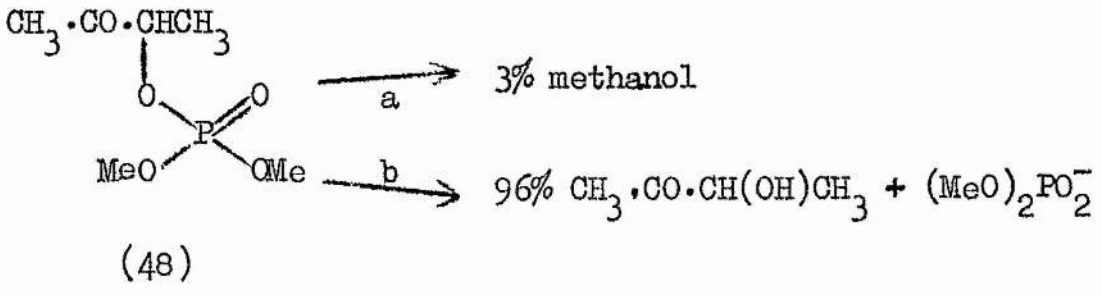
(46) (47)

The concurrent yield of the phosphoramidate with ethylene sulphide required the formation of the ester (47), which would lead to the O-phosphoryl ester and thence to the products. The S-phosphoryl ester, formed by the initial attack of the phosphorothioate ester on the epoxide, was postulated to be converted to the O-phosphoryl ester via a five-coordinate intermediate (47), in which pseudo-rotation occurred at a faster rate than expulsion of methoxide ion.

Frank and Usher[132] have used pseudo-rotation to explain the balance of reaction between two available pathways for dimethyl phosphoroacetoin (48) and the related methylphosphonoacetoin (49). Under basic catalysis, the carbonyl group transforms to a gem diol which, on deprotonation, attacks the phosphorus atom to yield a five-membered ring intermediate. The products formed are shown overleaf.

The change-over in preferred pathway was a result of the 200-fold decrease in the rate of path (b) for the methylphosphonoacetoin (49). This inhibition was explained by the restrictions that pseudo-rotation placed on the five-coordinate intermediate, together with the preferred equatorial configuration of the phosphoryl group. (Scheme 10.)

The pentacoordinate intermediate (50) resulted from apical



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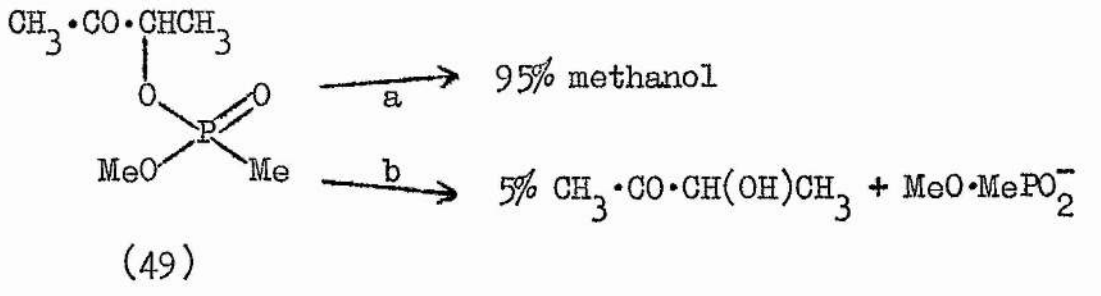
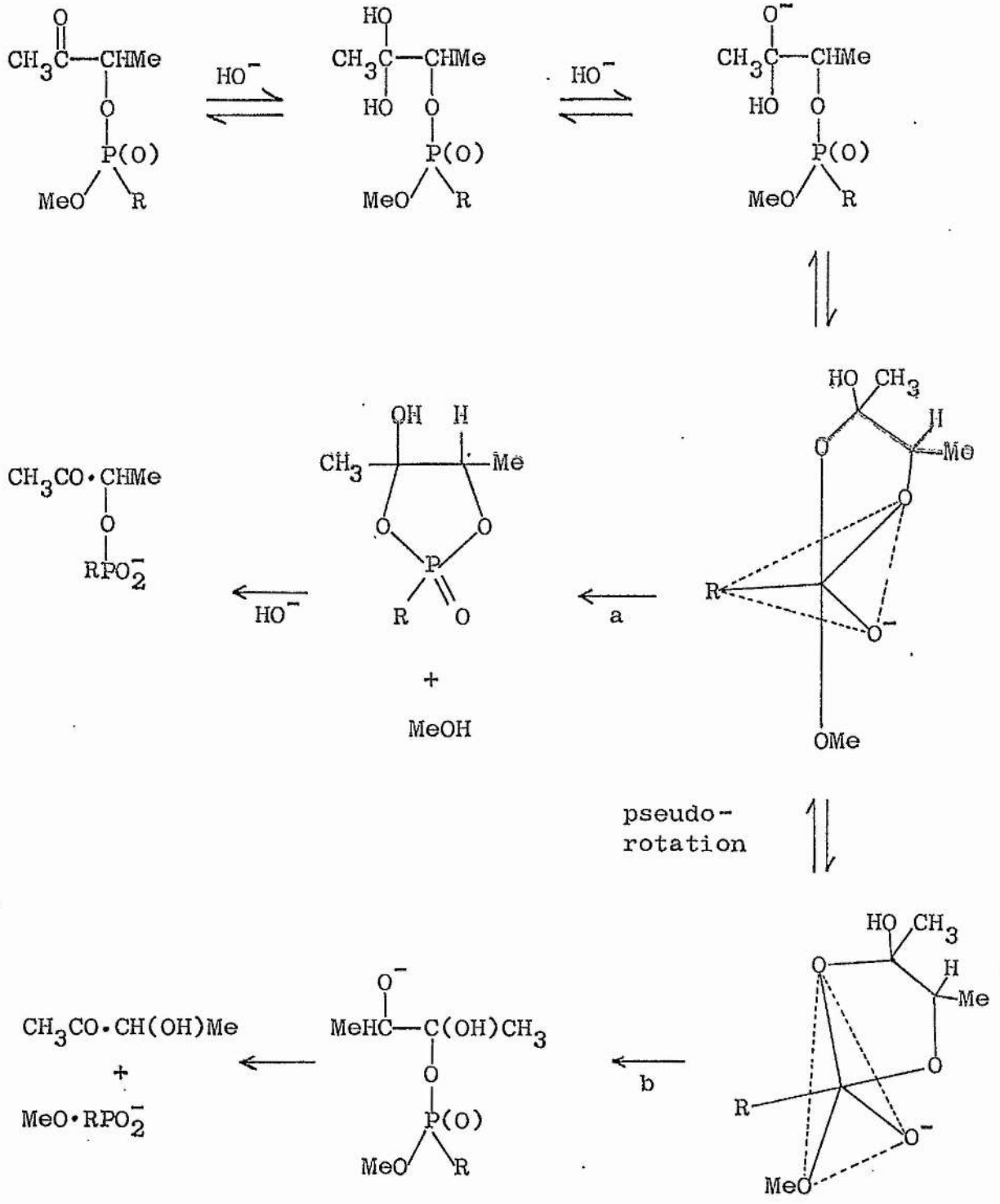


(49)

attack by the gem diol. Loss of methoxide ion, pathway (a), could occur without any of the constraints, that the ring lie axially-equatorially or that a carbon atom lie apically, being violated. For pathway (b), pseudo-rotation was necessary for the ring to leave from an apical position. There are no such restraints for the phosphoroacetoin (50; R=OMe) and (b) was observed to be the major pathway. However, for the methylphosphonoacetoin (50; R=Me) there is a violation of the constraint that a carbon atom cannot be placed apically and so pathway (b) should, as was experimentally verified, be inhibited.

Complementary evidence for the five-membered intermediate has been provided by Brown and Frearson[133] in their study of the rapid base hydrolysis of substituted dialkyl phosphoroacetoins



Scheme 10.

to acetoin and dialkyl phosphates. They discuss several possible pathways for the formation of the products, but conclude that in aqueous solution the only mechanism compatible with their experimental observations is an intramolecularly formed five-coordinate intermediate.

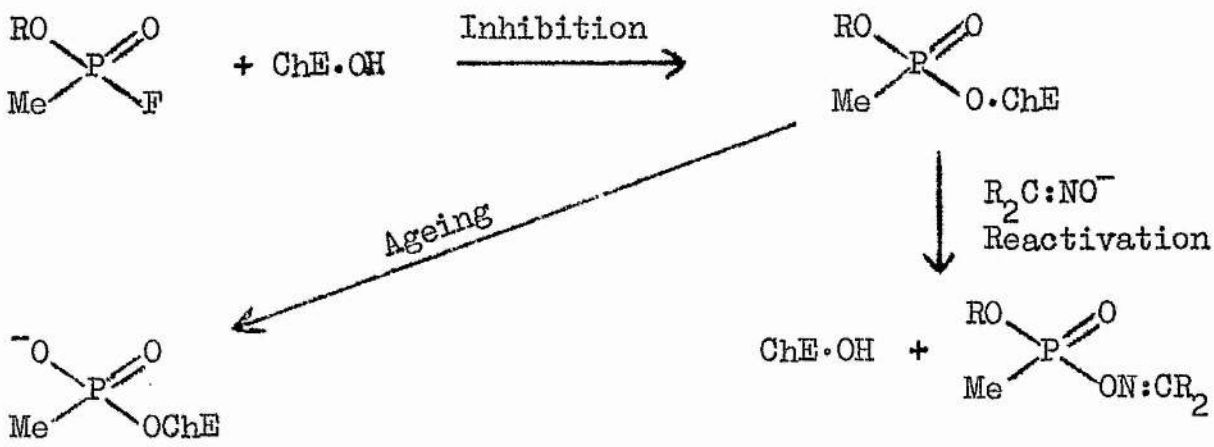
The Ageing of Phosphylated Acetyl Cholinesterases

It has been firmly established that the inhibition of acetyl cholinesterases and related enzymes by organophosphorus compounds is due to phosphylation at, or near, the active site of the enzyme molecule. The evidence for direct phosphylation is both stoicheiometric and kinetic.[134]

The inhibition can be reversed by hydrolysis to the free enzyme using powerful nucleophiles, such as oximes. In some cases, an initial rapid reactivation of the inhibited enzyme is followed by little change in the degree of reactivation. The change that occurs in the enzyme, to a form which cannot be reactivated, is termed "ageing".[135]

Further research revealed that ageing in the case of acetyl cholinesterases (ChE·OH) was caused by dealkylation of the phosphylated enzyme by acid catalysis, possibly from a protonated species in the enzyme.[136] Berends and his co-workers found that isopropanol was produced when diisopropyl phosphorofluoridate--inhibited pseudo-cholinesterase "aged".

Dealkylation of the phosphylated enzyme can occur (a) by bimolecular attack by a nucleophile on the α carbon of the alkyl group, or (b) by unimolecular fission of the alkyl oxygen bond to yield a carbonium ion and a phosphylate acid anion.



(resistant to $R_2C{:}NO^-$)

Ageing of phosphylated enzymes occurs more readily with secondary alkyl groups than those with primary alkyl groups. The lower reactivity of secondary as compared with primary alkyl groups towards bimolecular reaction with nucleophilic reagents has been confirmed in the dealkylation of primary and secondary dialkyl methylphosphonates with strong nucleophiles (I^- and $S_2O_3^=$).[138]

In a study designed to draw a comparison between the relative rates of hydrolysis of dialkyl methylphosphonates at 100° in 50% aqueous dioxan containing benzenesulphonic acid (1N) and the relative rates of ageing of phosphonylated acetyl cholinesterases, Cadogan and his co-workers[135] found a qualitative correspondence between the two sets of rates. Such a correspondence, coupled with unimolecular fission in the simple

phosphonates,[61,83,135] was believed to point to carbon-oxygen fission in the "ageing" process of phosphonylated enzymes.

Programme of Research

Cadogan and Maynard[139] had previously investigated the reaction of ethyl hydrogen methylphosphonate with p-nitrobenzonitrile oxide. This system was studied as a potential means of reactivating "aged" enzymes.

The 1:1 adduct of p-nitrobenzonitrile oxide and ethyl hydrogen methylphosphonate, ethyl α-hydroxyimino p-nitrobenzyl methylphosphonate, represented a model system where the "aged" enzyme was realkylated, with the concomitant formation of an oxime moiety in close proximity to the phosphorus atom. Cadogan and Maynard observed extremely rapid hydrolysis of the adduct to yield ethanol at pH 2-3·5, with anchimeric assistance of 2×10^7 times compared with the hydrolysis of a simple phosphonate, ethyl p-nitrophenyl methylphosphonate. The rate decreased after pH 3·5, and increasing quantities of p-nitroaniline were formed.

In view of the relevance of such a system to the reactivation of "aged" enzymes and of the most interesting rate acceleration observed, a more detailed study of this reaction was called for. This involved variation of the substituends at phosphorus

and extension of the reaction into solutions of greater pH.

As a supplement to work already in progress in this department,[135] the hydrolysis of ethyl pinacolyl methylphosphonate was studied, particularly to indicate the occurrence of a unimolecular hydrolysis by observing whether or not carbon-oxygen fission occurred.

EXPERIMENTAL

Page No.

EXPERIMENTAL

Proton Magnetic Resonance Spectroscopy

A Perkin-Elmer Model R-10 nuclear magnetic resonance spectrometer, operating at a frequency of 60 MHz. and a probe temperature of 35.5°, was used. Chemical shifts are recorded as tau (τ) values in parts per million, relative to tetramethylsilane (τ 10.0) as internal standard.

Elemental Analyses

Microanalyses were performed by Weiler and Strauss, Oxford, and by Mr. J. Bews, University of St. Andrews.

Other instruments were used which are described in the experimental section of Part I above.

Solvents and Purification of Materials

Dioxan was purified by the method of Vogel.[31c] Methylene chloride, chloroform, and carbon tetrachloride were dried by refluxing over phosphorus pentoxide before fractionation. Diethyl ether, referred to as ether, was dried by standing over sodium wire and fresh wire added after a week. Light petroleum (b.p. 40-60°), referred to as petrol, was dried over sodium wire.

Amines were dried by standing over potassium hydroxide pellets, before fractionation from fresh pellets. Alcohols were dried by refluxing over calcium hydride before distillation. Neopentyl alcohol and pinacol were dried by standing in ether solution over magnesium sulphate.

The Synthesis of the 1:1 Adducts of p-Nitrobenzonitrile oxide and the Phosphorus Acids

p-Nitrobenzhydroxamoyl Chloride

The oxime of p-nitrobenzaldehyde was prepared by the method of Vogel [31b] and crystallised from aqueous ethanol. The hydroxamoyl chloride was prepared by chlorination of the oxime (m.p. 128°) in chloroform solution at -10° using dry chlorine,[140,141] and crystallised from benzene (m.p. 125-126°). Bianchetti [141] and his co-workers reported 116°.

p-Nitrobenzonitrile Oxide

The hydroxamoyl chloride (8 g.), in dry ether solution (200 ml.), was treated with an equimolar quantity of triethylamine (4.5 g.) at 0°, with vigorous mechanical stirring. The precipitate was washed thoroughly with water to remove base hydrochloride and the remaining light-yellow nitrile oxide dried repeatedly over phosphorus pentoxide under high vacuum, until the i.r. spectrum

showed an absence of hydroxylic stretching frequencies at 3500 $cm.^{-1}$

The m.p. depended on the rate of heating. Thermal dimerization to the furoxan (m.p. 185-195°) sometimes occurred on slow heating. Grundmann[142] gives m.p. for the di-p-nitrophenyl furoxan as 199-201°. Rapid heating of the nitrile oxide gave m.p. 93°. Grundmann[142] gives m.p. 95°.

Phosphorus-containing Compounds

Alkyl methylphosphonochloridates

These were in general prepared by adding the alcohol (1 mole) with triethylamine (1 mole) to a vigorously stirred solution of the methylphosphonic dichloride (1 mole) (kindly supplied by C.D.E.E. Porton Down) in ether at 0°. After the addition, the solution was allowed to warm to room temperature, the base hydrochloride filtered off, and the chloridate obtained by distillation under reduced pressure. The method of Cadogan[143] was used for the preparation of pinacolyl methylphosphonochloridate (Table 16).

Other Chloridates

Diethyl phosphorochloridate was prepared by chlorinating redistilled diethyl phosphite at -10° in carbon tetrachloride solution.[147] The physical constants are reported in Table 16.

TABLE 16: Physical Constants of Some Phosphyl Chloridates, $R'RP(O)Cl$

R	R'	b.p.°/mm.	Refractive index n_D^{25}	Reported Values b.p.°/mm., n_D^{18} =	Reference
OMe	Me	54/4	*1.4322	73/22, 1.4395	144
OEt	Me	44/2.5	1.4320	32/1, 1.4385	144,145
OPr	Me	52/2	1.4320	94/21, 1.4378	144
OPr^i	Me	44/0.6	1.4290	83/22, **1.4285	144
$OCH_2.Bu^t$	Me	68/1	1.4309	51/0.08 -	146
$OCHMe.Bu^t$	Me	52/0.01	***1.4413	52-54/0.02, 1.4430	143
OEt	Ph	98/0.05	1.5368	103/0.3 -	145
OEt	OEt	80-81/9	1.4143	93-95/18 -	147
OEt	Bu^t	32/0.5	1.4352	new compound	
EtO	Pr^i	89/23	1.4355	53/1.9, 1.4357‡	148

* at 22° *** at 21°
** at 23° ‡ at 25°

Ethyl t-butylphosphonochloridate: Kinnear and Perren's method[149] was used to prepare t-butylphosphonic dichloride, a violet solid with a strong eucalyptus-like odour. The crude product was sublimed (110°/7 cms.) and had m.p. 112°. Kinnear[149] reported m.p. 110°.

Ethyl t-butylphosphonochloridate was prepared by adding sodium ethoxide (80 m.moles, 5.44 g.) in suspension-solution (150 ml.

benzene) to the above-prepared dichloride (12.9 g., 74 m.moles), with vigorous mechanical stirring in refluxing benzene during one hour. After removal of benzene, the ether solution was filtered through hyflo-supercel and the product obtained by distillation (Table 16). (Found: C, 38.6; H, 7.8. $C_6H_{14}ClO_2P$ requires C, 39.0; H, 7.6%.)

Ethyl isopropylphosphonochloridate: The chloridate (Table 16) was prepared analogously from isopropylphosphonic dichloride[149] (b.p. 75-76°/23 mm. Clay[150] reported 76°/23 mm.) with a shorter reflux time of ¼ hour.

Diethyl ethylphosphonate

The ester was obtained by distillation from the Arbusov reaction between ethyl iodide and triethyl phosphite,[151] b.p. 75-79°/8 mm.; n_D^{25}, 1.4137. Ford-Moore[151] reported 62°/2 mm.; n_D^{18}, 1.4172.

Ethyl diethylphosphinate

Kosolapoff and Watson's method[152] using thiophosphoryl chloride and ethyl magnesium bromide gave poor yields (3%) of the silver salt of diethylphosphinic acid. A more successful preparation was that of Sander,[153] based on the reaction of ethyl dichlorophosphite and ethyl magnesium chloride.

Ethanol (43 g., 0.94 mole) in ether was added dropwise (2 hrs.) to freshly distilled phosphorus trichloride (128 g., 0.93 mole) in ether (50 ml.) under a nitrogen atmosphere, with magnetic stirring at -20°. Stirring was continued for a further 9 hours as the flask warmed to room temperature. Ethyl dichlorophosphite (b.p. 116-118°; n_D^{20}, 1.4625. Steyermark [154] reported b.p. 116-118°; $n_D^{19.5}$, 1.4628) was obtained by distillation through a 2' column packed with glass helices at an outer jacket temperature of 102° in 42% yield (58.6 g.).

Ethoxy diethylphosphine (18%; b.p. 42°/20 mm.; n_D^{25}, 1.4351. Sander [153] reported b.p. 51°/67 mm.; n_D^{20}, 1.4403) was prepared from ethyl dichlorophosphite and ethyl magnesium chloride according to Sander's [153] method.

Ethyl diethylphosphinate was obtained by oxidation of the phosphine (3 g.) with 10% v/v hydrogen peroxide (10 ml.) in aqueous solution at 0°. The solution was stirred for ½ hour and then allowed to warm to room temperature. The ester was not isolated, but hydrolysed <u>in situ</u> to the sodium salt of diethylphosphinic acid.

<u>Alkyl Hydrogen Alkylphosphonates</u>

In general, the acids were obtained by hydrolysis of the corresponding chloridate.

Alkyl methylphosphonochloridates and diethyl phosphorochlori-

date were hydrolysed by their dropwise addition to vigorously stirred ice-water mixtures. More forcing conditions were used for chloridates whose structure would lead to slow rates of hydrolysis in ice-water mixtures (Table 17).

TABLE 17: Hydrolyses of Phosphorus Acid Chloridates. $(R'O)RPO.Cl)$

R'	R	Conditions of Hydrolysis
$Bu^t.CH_2$	Me	Sodium hydroxide (2M), 60°, 2 hours
$Bu^t.CHMe$	Me	Sodium hydroxide (2M), 60°, 2 hours
Et	Pr^i	Sodium hydroxide (2M), 40°, ½ hour
Et	Bu^t	Sodium hydroxide (2.7M), 40°, 14 hours followed by 5M, 70°, 4 hours.

Diethyl ethylphosphonate and ethyl diethylphosphinate were hydrolysed in sodium hydroxide solution (4.5M) at 80° for 3 hours. On cooling, all of the alkaline solutions were acidified and the water removed at the rotatory evaporator with the bath temperature $\not> 35°$. The residue was extracted with chloroform, the extract dried over sodium sulphate (12 hrs.), and the acids obtained by distillation (Table 18).

The equivalent weights of the acids were determined by titration and agreed within 3% of the calculated expected value.

Ethyl hydrogen phenylphosphonate was not distilled, but used immediately to form the adduct with p-nitrobenzonitrile oxide. as Kosolapoff[155] reported the compound to be unstable. The structure of the acid was confirmed by n.m.r. spectroscopy. ($CCl_4/CDCl_3$) τ-2.96 (singlet, POH, 1H), τ2.0-2.8 (complex multiplet, P-Ph, 5H); τ6.02 (quartet, $POCH_2CH_3$, 2H); and τ8.79 (triplet. $-CH_2CH_3$, 3H).

TABLE 18: Alkyl Hydrogen Alkylphosphonates and Related Compounds, $RR'PO_2H$

R	R'	b.p.°/mm.	Refractive Index, n_D^{25}	Reported Values b.p.°/mm.; n_D^{20} =	Reference
MeO	Me	92/0.1	1.4250*	104/0.1; 1.4248	156
EtO	Me	110/0.05	1.4219	106-107/0.1; 1.4258	156
PrO	Me	106/0.05	1.4259	104-105/0.05; 1.4282	156
Pr^iO	Me	88/0.02	1.4210	97-98/0.08; 1.4228	156
Bu^tCH_2O	Me	110/0.02	1.4250	New compound‡	
Bu^tCHMeO	Me	98/0.05	1.4320	116-118/0.1; 1.4322**	143
EtO	EtO	120/0.06	1.4140	-	
EtO	Et	92/0.04	1.4281	-	
EtO	Bu^t	72-76/0.03	1.4253	New compound‡	
EtO	Ph	‡	1.5223	-	
EtO	Pr^i	80-82/0.05	1.4199	New compound‡	
Et	Et	160°/0.03	1.4551ø	194-195/21	157

* 18°. ** 25°.
‡ see text. ø 20°.

The following three acids were new compounds, and had satisfactory analyses:- Ethyl hydrogen t-butylphosphonate (Found: C, 43.3; H, 9.6. $C_6H_{15}O_3P$ requires C, 43.3; H, 9.1%). Ethyl hydrogen isopropylphosphonate (Found: C, 39.1; H, 8.7. $C_5H_{13}O_3P$ requires C, 39.5; H, 8.6%). Neopentyl hydrogen methylphosphonate (Found: C, 43.9; H, 9.0. $C_6H_{15}O_3P$ requires C, 43.4; H, 9.1%).

4,4,5,5-Tetramethyl-2-oxo-2-hydroxy-1,3,2-dioxaphospholan

This compound has previously been prepared by Newton, Cox and Bertrand [126] and called "hydrogen pinacol phosphate", although not characterised.

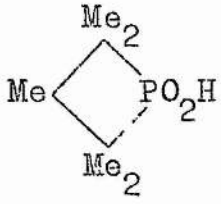
4,4,5,5-Tetramethyl-2-methoxy-1,3,2-dioxaphospholan was prepared by the method of Arbusov and Azanovskaya [158] from pinacol and phosphorus trichloride. The pure product (26%) was obtained after two distillations, b.p. 80-81°/22 mm.; n_D^{25}, 1.4357. Arbusov and Azanovskaya [158] reported b.p. 91-92.5°/48 mm.; n_D^{20}, 1.4417.

The phosphite was quantatively oxidised [159] to the phosphate ester using dinitrogen tetroxide in methylene chloride at -70°. On removal of solvents under reduced pressure, 4,4,5,5-tetramethyl-2-oxo-2-methoxy-1,3,2-dioxaphospholan was obtained as a light yellow solid, m.p. 88-90° (Found: C, 43.1; H, 7.7. $C_7H_{15}O_4P$ requires C, 43.3; H, 7.8%). The i.r. spectrum was consistent with

the structure of the compound (nujol mull): 1272 (ν P=O, s), 1141 (ν POMe, s), 1050 and 970 $cm.^{-1}$ (ν POC, s).

The exocyclic acid was obtained by hydrolysis of the ester in 50% aqueous dioxan for two hours at room temperature. After removal of the solvents under reduced pressure, 4,4,5,5-tetramethyl-2-oxo-2-hydroxy-1,3,2-dioxaphospholan was obtained as a slightly off-white solid, m.p. 173° (Found: C, 40.0; H. 7.5. $C_6H_{13}O_4P$ requires C, 40.0; H, 7.3%).

Cyclic Phosphinic Acids



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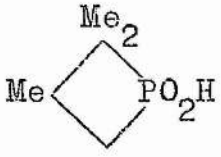

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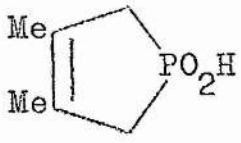

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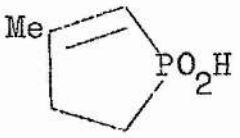

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1-Oxo-1-Hydroxy-2,2,3,4,4-Pentamethyl Phospha-cyclobutan (51)

The acid was obtained by the *in situ* hydrolysis of the chloride obtained from 2,4,4-trimethylpent-2-ene, anhydrous aluminium chloride, and redistilled phosphorus trichloride according to McBride's method.[160] The intermediate was decomposed in the manner directed, but an oil, rather than the solid reported by McBride, resulted after drying in methylene chloride solution over sodium

sulphate for 12 hours. The oil was hydrolysed in boiling water (350 ml.) for 3 hours, and concentration and cooling caused the acid to precipitate as white crystals. After crystallisation from petrol (60-80°), the anhydrous acid (m.p. 71-72°, McBride[160] reported 71°) was obtained by drying it above the melting point over phosphorus pentoxide under high vacuum.

1-Oxo-1-Hydroxy-2,2,3-Trimethyl Phospha-cyclobutan (52)

This was prepared analogously by substituting 2,3-dimethyl-but-1-ene as the olefin substrate. No attempt was made to isolate the acid chloride and after decomposition of the intermediate, the oil was boiled with water (250 ml.) for 75 minutes. During this time a white amorphous solid (22.7 g., m.p. > 240°) formed, which was filtered off, but not further characterised. On removal of water, the oil was dried and the acid obtained by distillation from glass-wool in a side-arm receiver at a block temperature 210°/ 0.05 mm. The acid, a faintly coloured oil which darkened on standing, was characterised as its cyclohexylamine salt, m.p. 184-185° (Found: C, 57.7; H, 10.4; N, 5.9. $C_{12}H_{26}NO_2P$ requires C, 58.3; H, 10.6; N, 5.7%).

1-Hydroxy-3,4-Dimethyl-3-Phospholene Oxide (53)

This product was prepared according to the method of Hunger[161] with the modification that in the preparation of the tribromophos-

phorane intermediate, the solution was allowed to remain at room temperature for a longer period of time. Freshly distilled phosphorus tribromide (103 g., 0.38 mole) was added dropwise (¾ hour) with stirring, to 2,3-dimethylbutadiene (35.2 g., 0.43 mole) in dry petrol (40-60°; 500 ml.) at a temperature between -15° and -10°. The solution was maintained at -10° for an hour, then warmed to room temperature, and kept for 5½ days at 15°. The hygroscopic solid which precipitated was immediately dissolved in methylene chloride (1 litre) and was esterified by the dropwise addition (1 hr.), with vigorous stirring at -10°, of a mixture of methanol and triethylamine (1.5 moles, based on 100% yield of phosphorane) dissolved in methylene chloride (100 ml.). The solution was warmed to room temperature with stirring (2 hrs.), solvents removed under reduced pressure, and the base hydrochloride filtered from a benzene solution. The methyl ester (21.8 g., 0.14 mole, 57%) was obtained by distillation, b.p. 66-76°/0.05-1 mm.; n_D^{20}, 1.4878. Arbusov[162] reported 131°/10 mm.; n, 1.4892.

The acid, which was not further purified, was obtained by hydrolysis of the methyl ester in boiling hydrochloric acid (1:1) for 12 hours.

It is generally agreed that the double bond does not migrate to the 2-position when it is substituted by two methyl groups in

the 3- and 4-positions.[161-163] Quin and his co-workers[163] have demonstrated the stability of 1,3,4-trimethyl-3-phospholene oxide by refluxing it with hydrochloric acid (3N). No change was detected after 18 hours and there was only slight reaction to yield two products after 72 hours. The isomers are separable by g.l.c.[163].

1-Hydroxy-3-Methyl-2-Phospholene Oxide (54)

Isoprene (22.2 g., 0.34 mole) and redistilled phosphorus trichloride (49.5 g., 0.34 mole) in methylene chloride (300 ml.) were kept at 20° for 18½ days. The colour deepened on standing, eventually becoming black. Addition of dry petrol (40-60°) precipitated a black oily solid, which was further washed with 3 portions of petrol. The adduct was esterified with methanol (1.2 moles) in the presence of triethylamine (1.2 moles) in methylene chloride (500 ml.) and the methyl ester distilled (b.p. 72-75°/0.05 mm.; n_D^{25}, 1.4902; 9.44g, 18%). Quin[163] and his co-workers reported 79°/0.4 mm.

The position of the double bond was found to lie in the 2-position by n.m.r. and i.r. spectroscopy. The n.m.r. spectrum of a 20% solution ($CDCl_3$) showed: τ4.08 (doublet, C=C-$\underline{H}$, J 24 Hz, 1H); 6.32 (doublet, POC$\underline{H}_3$, J_{POMe} 11 Hz, 3H); and 7.2-8.3 (complex multiplet, -C$\underline{H}_2$-, with a single sharp peak 7.99,

C-$\underline{CH}_3$, total 7H). The i.r. spectrum (liquid film) showed prominent peaks at 1610 (ν C=C, s), 1220 (ν P=O, s), 1040 (P-O-Me, s), 925 (m), 885 (m), and 800 (s) $cm.^{-1}$

Quin[163] reported the part-spectrum of the methyl ester and gave the position of the vinyl proton doublet as τ 3.7, J=24 Hz. He also reported that the i.r. frequency of ν C=C was generally lower and more intense for the 2-isomer than the 3-isomer. The frequency observed above is in good agreement with the value observed for the related 1,3-dimethyl-2-phospholene oxide.

The acid was obtained by hydrolysis of the ester in boiling hydrochloric acid (1:1) for $3\frac{3}{4}$ hours. After removal of water under reduced pressure, the acid was dried and distilled (block temperature 230-260°/0.12 mm.) to yield a yellow oil, which partly solidified on standing. The i.r. spectrum (liquid film) showed peaks characteristic of an acid thus: 2700 and 2280 (broad, ν POH), 1600 (ν C=C), 1180 and 1160 $cm.^{-1}$ (ν PO_2^-).

Alkyl α-hydroxyimino-p-nitrobenzyl alkylphosphonates

It was essential for the preparation of these 1:1 adducts of p-nitrobenzonitrile oxide and a phosphyl acid for all chemicals, solvents, and apparatus to be rigorously dry. A dry box, in which weighing and filtration operations could be carried out, was used throughout the preparation of these adducts.

The preparation of pinacolyl α-hydroxyimino-p-nitrobenzyl methylphosphonate was typical of the procedure followed.

Pinacolyl hydrogen methylphosphonate (3.24 g., 18 m.moles dried in dioxan solution [20 ml.] over sodium sulphate) was mixed with p-nitrobenzonitrile oxide (5.5 g., 34 m.moles) in dioxan (150 ml.) and allowed to stand for 24 hours at room temperature in a light-protected flask. The dioxan was removed at room temperature ($\div 25^{\circ}$) and 0.05 mm. pressure to leave a solid residue. This residue was extracted with pinacolyl alcohol to leave a pale yellow residue, which was washed with ether and dried by drawing nitrogen through it in the dry box. The solid was identified as di-p-nitrophenylfuroxan (3.2 g., 58% based on the nitrile oxide) by its identical i.r. spectrum to that of an authentic sample.

The alcohol solution was evaporated at room temperature and 0.05 mm. pressure, and ether (25 ml.) with a little petrol ($40\text{-}60^{\circ}$, 5 ml.) added to precipitate a light yellow solid. The solid adduct (2.3 g., 6.7 m.moles, 37% based on acid taken) was washed with ether, and again dried by drawing nitrogen through it in the dry box.

The structure of pinacolyl α-hydroxyimino-p-nitrobenzyl methylphosphonate was confirmed by n.m.r. and i.r. spectroscopy. The i.r. spectrum showed the presence of NOH (ν NOH, 3100-3140 $cm.^{-1}$),

aromatic ring (ν ring 1600 and σ ring 850 $cm.^{-1}$), NO_2 (ν NO_2, 1515 and 1350 $cm.^{-1}$), phosphorus bonding (ν P=O 1230, ν POEt 1035 $cm.^{-1}$) and oxime (ν C=N, 1635 $cm.^{-1}$) moieties.

The n.m.r. spectrum showed the correct integral for each of the proton species and each of the absorptions to be expected for the 1:1 adduct - ($CDCl_3$): τ1.78 (centre of AA'BB' quartet, 4H); τ5.58 (quintet, methine C-H, 1H); τ8.21 (centre of doublet, P-CH_3, J_{PMe} 18 Hz, 3H; τ8.65 (quartet, lone methyl, HC-CH_3, 3H); and τ9.05 (singlet, t-Bu, 9H).

The analysis was that expected:- Found: C, 49.0; H, 6.0; N, 8.4. $C_{15}H_{21}N_2O_6P$ requires C, 48.8; H, 6.1; N, 8.1%.

The ratio of nitrile oxide:acid of 2:1 was found to give the optimum yield bearing in mind the competing dimerization of the nitrile oxide and the formation of the adduct as a clean, dry solid.

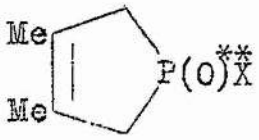
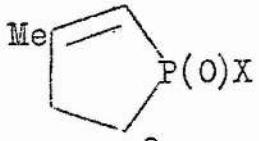
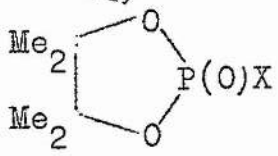
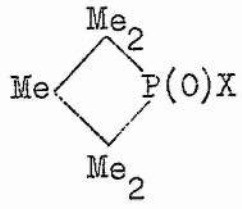
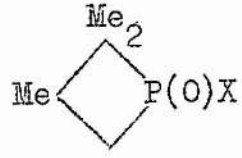
It was necessary to use the alcohol corresponding to the ester moiety for the work-up to prevent transesterification. Where the corresponding alcohol was solid, the initial residue was extracted with ether (4 x 75 ml.). Preparative details for the remaining adducts are tabulated (Table 19).

The structures of all of the 1:1 adducts were confirmed by spectroscopy (Table 20) and the compounds had satisfactory elemental analyses (Table 21).

TABLE 19: Preparation of the 1:1 adducts, $RR'P(O)OC(p\text{-}O_2NC_6H_4)=NOH$, from p-Nitrobenzonitrile oxide and Phosphyl acids

R	R'	nitrile oxide (g., m.moles)	acid (g., m.moles)	dioxan (ml.) and time (hrs.)	yield furoxan (g., %)	yield adduct (g., %)	m.p. °C
MeO	Me	5.2, 32	2.0, 20	110, 24	1.62, 31	2.3, 40	115
EtO	Me	3.26 20	1.24, 10	100, 24	1.34, 41	0.69, 27	130
PrO	Me	4.5, 27	1.95, 14	100, 24	1.85, 41	2.0, 46	88-90
$Pr^{i}O$	Me	5.0, 30	2.1, 15	120, 24	3.84*	1.4, 30	112-4
$Bu^{t}CH_2O$	Me	5.6, 35	3.0, 18	100, 24	2.1, 39	3 50	110
$Bu^{t}CHMeO$	Me	5.6, 35	3.24, 18	100, 48	3.2, 58	3.3, 55	110-3
EtO	EtO	5.4, 33	2.62, 17	100, 24	wt. not recorded	1.16, 20	94.5-95
EtO	Et	5.5, 33	2.3, 17	100, 24	2.3, 42	1.37, 27	98-100
Et	Et	3.5, 21	1.7, 11	120, 24	2.1, 59	0.52, 17	112
EtO	Bu^{t}	2.15, 13	1.5, 9	100, 24	0.73, 34	0.82, 19	114
EtO	Ph	5.9, 36	3.1, 18	100, 24	2.4, 41	1.5, 24	142-3

TABLE 19 (contd.)

Adduct	nitrile oxide (g., m.moles)	acid (g., m.moles)	dioxan (ml.) and time (hrs.)	yield furoxan (g., %)	yield adduct (g., %)	m.p.°
	4, 24	1.7, 11.6	100, 72	1.5, 38	1.58, 44	127
	1.9, 11	0.65, 5	60, 24	0.85, 50	0.52, 36***	118-120
	4.3, 26	2.3, 13	100, 24	not recorded	0.74, 16	166-8
	5.1, 31	2.86, 16	100, 60	0.3, 6	4.3, 78	125
	4.0, 24	1.79, 12	120, 12	0.83, 21	0.5, 13	118-120

* a mixture of di-p-nitrophenyl furoxan and the 1:1 adduct.

** X = OC(p-$NO_2C_6H_4$)=NOH.

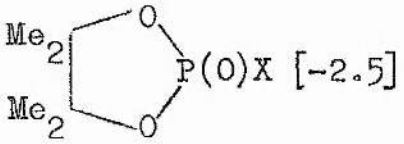
*** initially precipitated as an oil, but solidified after a week.

TABLE 20: Proton Magnetic Resonance Data for the Alkyl α-hydroxyimino-p-nitrobenzyl phosphyl Adducts

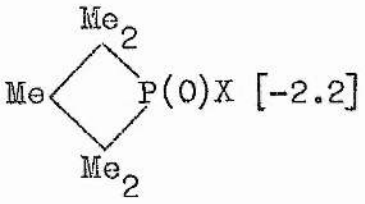
All spectra were run in deutero-chloroform on approximately 5% (saturated) solutions. The tau (τ) value quoted is that of the multiplet centre. Average coupling constants (J) were observed as follows: P-CH_3 18 Hz; $POCH_3$ 11 Hz; $POCH_2$ 7 Hz; and CH_3-CH_2 7 Hz. In a few cases, signals due to the oxime proton were recorded at about τ -2. Compounds for which such signals were observed are listed below (τ value in brackets, and X = $-OC(\underline{p}\text{-}NO_2C_6H_4)=NOH$):-

$(EtO)Bu^tP(O)X$ [-2.3]

$(EtO)_2P(O)X$ [-1.8]

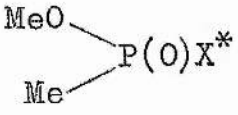


[-2.5]

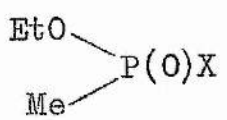


[-2.2]

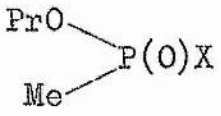
The methylene protons of the propyl ester moiety $CH_3C\underline{H}_2\,CH_2O$- overlapped with those of the PCH_3 moiety, indicated by ** in the table.



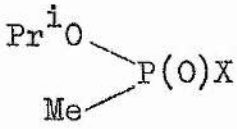
τ 1.78 (quartet, aromatic, 4H); τ6.10 (doublet , $POC\underline{H}_3$, 3H) and τ8.20 (doublet, P-$\underline{Me}$, 3H).



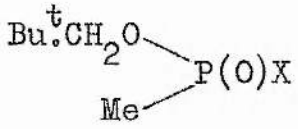
τ 1.73 (quartet, aromatic, 4H); τ 5.77 quintet, $POC\underline{H}_2CH_3$, 2H); τ 8.21 (doublet, P-$\underline{Me}$, 3H) and τ8.64 (triplet $POCH_2C\underline{H}_3$, 3H).



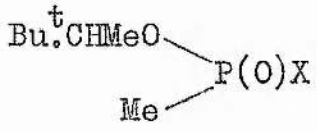
τ1.79 (quartet, aromatic, 4H); τ5.84 (quartet, $POC\underline{H}_2CH_2-$, 2H); τ8.21 (doublet, P-$\underline{Me}$, 5H**) and τ9.04 (triplet. $-CH_2C\underline{H}_3$, 3H).



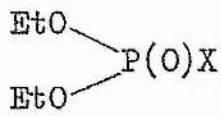
τ1.78 (quartet, aromatic, 4H); τ5.1 (quintet of doublets, $POC\underline{H}$, 1H); τ8.25 (doublet, P-$C\underline{H}_3$, 3H) and τ8.43 (doublet of doublets, POCH-$C\underline{H}_3$, 6H).



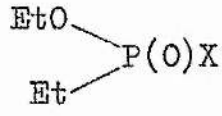
τ1.80 (quartet, aromatic, 4H); τ6.19 (doublet of doublets, $POC\underline{H}_2-$, 2H); τ8.21 (doublet, P-$\underline{Me}$, 3H) and τ9.07 (singlet, C-$(C\underline{H}_3)_3$, 9H).



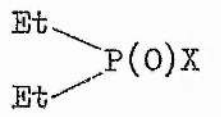
τ1.78 (quartet, aromatic, 4H); τ5.59 (quintet, $POC(Me)\underline{H}$, 1H); τ8.21 (doublet, P-$\underline{Me}$, 3H); τ8.65 (quartet, POC.H.$C\underline{H}_3$, 3H) and τ9.05 (singlet, $C(C\underline{H}_3)_3$, 9H).



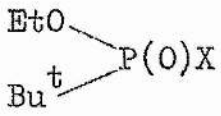
τ1.77 (quartet, aromatic, 4H); τ5.62 (quintet, $POC\underline{H}_2CH_3$, 4H) and τ8.85 (triplet, $POCH_2C\underline{H}_3$, 6H).



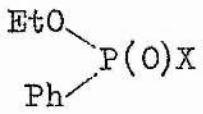
τ1.83 (quartet, aromatic, 4H); τ5.75 (quintet, $POC\underline{H}_2CH_3$, 2H); τ7.79 (septet, $PC\underline{H}_2CH_3$, 2H); τ8.52 (triplet, $PCH_2C\underline{H}_3$, 3H) and τ8.90 (triplet, $POCH_2C\underline{H}_3$, 3H).



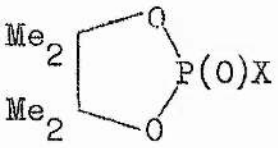
τ1.82 (quartet, aromatic, 4H); τ8.04 (septet, $PC\underline{H}_2CH_3$, 4H) and τ8.64 (triplet, $PCH_2C\underline{H}_3$, 6H).



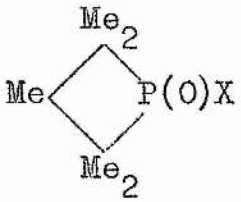
τ 1.80 (unresolved, aromatic, 4H); τ 5.77 (quintet, $POC\underline{H}_2CH_3$, 2H) and τ 8.52-8.80 ($POCH_2C\underline{H}_3$ and $C(C\underline{H}_3)_3$, 12H).



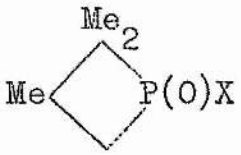
τ 1.95 (quartet, aromatic, $C_6\underline{H}_4NO_2$) and τ 2.0-2.8 (complex multiplets, P-$C_6\underline{H}_5$, total aromatic protons, 9H); τ 5.68 (quintet, $POC\underline{H}_2CH_3$, 2H) and τ 8.62 (triplet, $POCH_2C\underline{H}_3$, 3H).



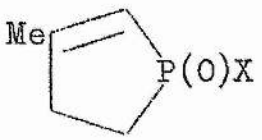
τ 1.73 (quartet, aromatic) and τ 8.59 (singlet, $C(C\underline{H}_3)_2$).



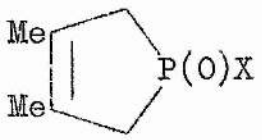
τ 1.92 (quartet, aromatic, 4H) and τ 8.0-9.1 (unresolved, aliphatics, 16H).



not run, insufficient material.



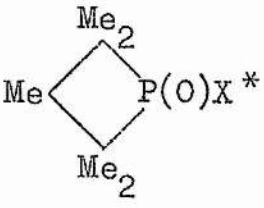
not run, insufficient material.

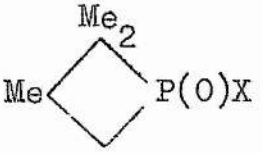


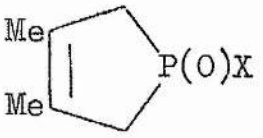
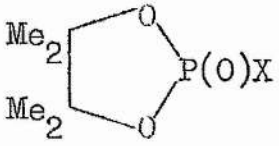
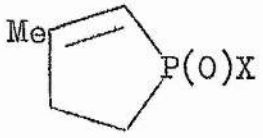
τ 1.92 (quartet aromatic. 4H) and τ 7.3, 7.92, 8.22. and 8.7 (unresolved multiplets, 10H).

* X = $-OC(\underline{p}\text{-}NO_2C_6H_4)=NOH$.

TABLE 21: Elemental Analyses for Alkyl α-hydroxyimino-p-nitrobenzyl Phosphyl Adducts, $RR'P(O)OC(p\text{-}NO_2C_6H_4)=NOH$

R	R'	Molecular Formula	Analyses: % Found / % Calculated
MeO	Me	$C_9H_{11}N_2O_6P$	C, 39.2; H, 4.0; N, 10.4.
			C, 39.4; H, 4.0; N, 10.2.
EtO	Me	$C_{10}H_{13}N_2O_6P$	C, 41.6; H, 4.7; N, 10.1.
			C, 41.7; H, 4.5; N, 9.7.
PrO	Me	$C_{11}H_{15}N_2O_6P$	C, 42.9; H, 5.0.
			C, 43.8; H, 5.0.
Pr^iO	Me	$C_{11}H_{15}N_2O_6P$	C, 43.0; H, 5.0; N, 8.9.
			C, 43.8; H, 5.0; N, 9.3.
Bu^tCH_2O	Me	$C_{13}H_{19}N_2O_6P$	C, 47.0; H, 5.5; N, 8.7.
			C, 47.3; H, 5.8; N, 8.9.
Bu^tCHMeO	Me	$C_{14}H_{21}N_2O_6P$	C, 49.0; H, 6.0; N, 8.4.
			C, 48.8; H, 6.1; N, 8.1.
EtO	EtO	$C_{11}H_{15}N_2O_7P$	C, 40.6; H, 4.5; N, 8.8.
			C, 41.5; H, 4.7; N, 8.7.
EtO	Et	$C_{11}H_{15}N_2O_6P$	C, 44.0; H, 5.0; N, 9.6.
			C, 43.7; H, 5.0; N, 9.3.
Et	Et	$C_{11}H_{15}N_2O_5P$	C, 45.6; H, 5.2; N, 10.0.
			C, 46.1; H, 5.3; N, 9.8
EtO	Bu^t	$C_{13}H_{19}N_2O_6P$	C, 47.6; H, 5.6.
			C, 47.3; H, 5.8.
		$C_{15}H_{21}N_2O_5P$	C, 52.8; H, 6.0; N, 8.1.
			C, 52.9; H, 6.2; N, 8.2.



	$C_{13}H_{17}N_2O_5P$	C, 49.8; H, 5.3; N, 9.2.
		C, 49.9; H, 5.5; N, 9.0.
	$C_{13}H_{15}N_2O_5P$	C, 50.0; H, 4.7; N, 8.9.
		C, 50.0; H, 4.9; N, 9.0.
	$C_{13}H_{17}N_2O_7P$	C, 45.4; H, 5.0; N, 8.2.
		C, 45.3; H, 5.0; N. 8.1.
	$C_{12}H_{13}N_2O_5P$	C, 48.8; H, 4.1.
		C, 48.7; H, 4.4.

*X = $-OC(p\text{-}O_2NC_6H_4)=NOH$

Infra-Red Spectra

The spectra of the adducts were obtained from nujol mulls and confirmed the structures of the 1:1 adducts. The principal groups in the adducts showed frequencies at 3100 $cm.^{-1}$ (w, ν NOH), 1600 $cm.^{-1}$ (m-s, ν aromatic ring), 1520 and 1350 $cm.^{-1}$ (s, ν NO_2), 1180-1250 $cm.^{-1}$ (s, ν P=O) and 850 $cm.^{-1}$ (s, δ NO_2). The phosphoryl group absorption was generally around 1230 $cm.^{-1}$, but lower values were observed for the phosphinate adducts.[39]

Variation in the position of the oxime C=N stretching

frequency was observed. The alkyl methylphosphonate adducts had ν C=N values of about 1630 $cm.^{-1}$, which is at the lower end of the generally accepted range of oxime stretching values. All of the other adducts showed values of ν C=N of 1690-1700 $cm.^{-1}$, which is at the upper limit of observed oxime stretching frequencies.[39] Methyl α-hydroxyimino-p-nitrobenzyl methylphosphonate was unique in that it showed values at 1630 and 1700 $cm.^{-1}$ Concomitant with the increase in the ν C=N frequency was the increase in the intensity of the NOH absorption at 3100 $cm.^{-1}$ from being of previously weak intensity to weak-medium intensity.

Attempted Preparation of Ethyl α-hydroxyimino-p-nitrobenzyl isopropylphosphonate

The preparation was tried on two occasions in a manner analogous to that described for the pinacolyl methylphosphonate adduct. p-Nitrobenzonitrile oxide (3.8 g., 23 m.moles) and ethyl hydrogen isopropylphosphonate (1.8 g., 12 m.moles) yielded di-p-nitrofuroxan (2.6 g., 70%) and, from the ethanol extract, about 70 m.g. of a yellow, oily solid. The i.r. spectrum showed it not to be the desired adduct.

Preparation of 4,4,5,5-Tetramethyl-2-oxo-2-(α-hydroxyimino -p-nitrobenzoxy)-1,3,2-Dioxaphospholan

The preparation of this adduct was attempted on three

separate occasions (Table 19). The first preparation initially yielded 0.74 g. of a compound, which had the correct n.m.r. signals, but a poor proton ratio and a poor elemental analysis. Further washing with ether in the dry-box yielded a smaller quantity of solid (about 0.2 g.), which had a correct elemental analysis, but whose spectral characteristics were not determined. The compound was not systematically investigated and was found to have decomposed after a month.

The compound was not able to be synthesised on two further occasions.

Solvolytic Behaviour of the Adducts

The adducts exhibited varying behaviour on hydrolysis at various pH. In acid solution the phosphonate and phosphate adducts were rapidly hydrolysed to lose the ester moiety, while in alkaline solution p-nitroaniline was formed.

Product Analysis

(a) Acid hydrolysis

The products of hydrolysis were followed by n.m.r. spectroscopy. To a solution of the alkylphosphonate adduct in deutero-chloroform was added 4 drops of deuterium oxide, the mixture shaken, and left for a day at room temperature. The solid acid,

hydrogen α-hydroxyimino-p-nitrobenzyl alkylphosphonate, was filtered, dried, and identified by comparison of its identical and superimposable i.r. spectrum to that of an authentic sample. The p.m.r. spectrum of the filtrate showed only signals due to the alcohol resulting from hydrolysis (Table 22).

In the case of pinacolyl α-hydroxyimino-p-nitrobenzyl methylphosphonate, the presence of pinacolyl alcohol was shown by (a) its retention time on two g.l.c. columns (10% PEGA, 66°, hydrolysate and authentic pinacolyl alcohol, 1 peak, retention time 10 minutes: 15% DNP, 56°, hydrolysate and authentic pinacolyl alcohol, 1 peak, retention time 29.6 minutes), and (b) the identical nature of the urethane of the hydrolysate and that of authentic pinacolyl alcohol. The urethanes were made by mixing p-chlorophenyl isocyanate and the alcohol, and were purified by elution with 75% benzene-petrol from an alumina column. The compounds had superimposable i.r. spectra, m.p. and mixed m.p. 101.5-102.5°. None of the olefins obtained from the acid hydrolysis of ethyl pinacolyl methylphosphonate was able to be detected by g.l.c. using the described conditions (page 169).

The solids filtered from the hydrolyses of ethyl α-hydroxyimino-p-nitrobenzyl, ethylphosphonate and phenylphosphonate had i.r. spectra similar to hydrogen α-hydroxyimino-p-nitrobenzyl methylphosphonate, 2300 $cm.^{-1}$ (ν POH, shallow), 1650 (ν C=N),

TABLE 22: N.m.r. Spectra of Soluble Hydrolysis Products of $RR'P(O)OC(p\text{-}NO_2C_6H_4)=NOH$ in $D_2O/CDCl_3$

R	R'	P.m.r. Signals (τ value) and Assignment
MeO	Me	6.52 (singlet, $C\underline{H}_3OH$)
EtO	Me	6.29 (quartet, $CH_3C\underline{H}_2O$-, 2H) and 8.78 (triplet, $C\underline{H}_3CH_2$-, 3H)
PrO	Me	6.38 (triplet, $-CH_2C\underline{H}_2OH$, 2H); 8.44 (sextet, $-CH_2C\underline{H}_2CH_3$, 2H) and 9.06 (triplet, $C\underline{H}_3CH_2$-, 3H)
Pr^iO	Me	8.80 (doublet, J_{HH} 8 Hz)*
$Bu^t.CH_2O$	Me	6.70 (singlet, $Bu^t.C\underline{H}_2O$-, 2H) and 9.09 (singlet, $\underline{Bu}^t$, 9H)
EtO	Et	6.25 (quartet, $CH_3C\underline{H}_2O$-, 2H) and 8.76 (triplet, $C\underline{H}_3CH_2O$-, 3H)
EtO	EtO	6.29 (quartet, $CH_3C\underline{H}_2O$-, 2H) and 8.78 (triplet, $C\underline{H}_3CH_2O$-, 3H)
EtO	Ph	6.30 (quartet, $CH_3C\underline{H}_2O$-, 2H) and 8.78 (triplet, $C\underline{H}_3CH_2O$-, 3H)

*the methine proton could not be distinguished against the background noise.

1600 (ν aromatic), 1530 and 1350 (νNO_2) and ν P=O (1250 P-Ph and 1162 P-Et). They both titrated as dibasic acids and the following equivalent weights were determined:-

P-Et compound. Found: 136; expected 137.

P-Ph compound. Found: 158; expected 161.

The products are thus considered to be the acid resulting from hydrolysis of the ester moiety (Table 22).

(b) Alkaline hydrolysis

The solutions were bright yellow and had u.v. spectra showing absorptions with λ_{max} 380–382 (λ_{max} p-nitroaniline 382 nm.). The solutions, when run on t.l.c. plates (silica or alumina coated, ether developer, chromogenic detection by iodine vapour or p-dimethylamino benzaldehyde, R_f values about 0.5), showed only one spot, which was identical to that of p-nitroaniline.

Propyl α-hydroxyimino-p-nitrobenzyl methylphosphonate (0.41 g., 1.41 m.moles) was decomposed in 98% aqueous dioxan buffer, pH 9.2, at room temperature for 6 hours. The solvents were removed under reduced pressure and the residue extracted with chloroform and ethyl methyl ketone to leave a white, water-soluble solid m.p. > 260° which was the salt components of the buffer. The organic extract was chromatographed on alumina and p-nitroaniline (0.18 g., 93%), m.p. 147° and mixed m.p. 149°, eluted with 50% ether-ethyl acetate.

No pinacolyl alcohol could be detected by g.l.c. after pinacolyl α-hydroxyimino-p-nitrobenzyl methylphosphonate was allowed to decompose in aqueous dioxan buffer, pH 9.20, and p-nitroaniline was again recovered in 83% yield.

Quantative Determination of the Yields of p-Nitroaniline

The extinction coefficient for p-nitroaniline at the position of maximum absorption (λ_{max} 382 nm.) was found to be 13,460 in 0.16% dioxan-water.

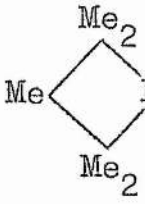
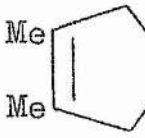
Known weights of p-nitroaniline (12.7 and 14.5 m.g.) were dissolved in dioxan (2 ml.), sodium chloride solution (0.1M, 50 ml.) added, and its pH adjusted to 8.43 by the addition of sodium hydroxide solution (0.05 ml., 0.1M). The solutions were diluted with water (x 25) and the optical density determined (0.955 and 1.08) at 382 nm.

In the alkaline decomposition of the adducts, a known quantity of compound was dissolved in dioxan (2 ml.) and a portion (1 ml.) was introduced by a pipette into the titration vessel of the Radiometer assembly containing sodium chloride solution (25 ml., 0.1M) and allowed to react for 10 half-lives at pH 8.43. The volumes of titrant added were recorded. The optical density of the hydrolysate was determined on a sample made by withdrawing 1 ml. of the solution and diluting with water (x 25) (Table 23).

All of the compounds showed only the absorption at 382 nm. after 10 half-lives. The absorption at 268 nm. in the starting material had completely disappeared.

The values of the yields obtained are probably low because of

TABLE 23: Optical Densities for Alkaline Hydrolysis Solutions

Adduct	Wt. Taken (m.gms.)	pH	NaOH solution added (ml.)	Optical Density (382 nm.)	Yield p-nitroaniline %
	30.3	8.43	1.6	0.780	83
	34.1	8.50	1.35	0.593	83
$Et_2P(O)X$	27.6	8.50	2.34	0.708	79
EtO.EtP(O)X	21.8	8.50	2.48	0.146***	85
EtO.PhP(O)X	22.7	8.50	1.50	0.531	84
EtO.Bu^tP(O)X	28.4	8.53	1.86	0.766	93
$(EtO)_2P(O)X$	20.0	8.53	0.69	0.470	75

*X = $-OC(p\text{-}O_2NC_6H_4)=NOH$.

**an additional 1 ml. of methanol was added to increase the solubility.

***final solution diluted by a further factor of 10.

(a) the necessity that the tared container had to be handled in the dry box while it was being roughly weighed and filled prior to removal, and accurate weighing on an analytical balance, and (b) the

design of the titration cell did not allow the pipette to drain completely after delivery of the solutions. Experiments in which the difference in weight between not allowing the pipette to drain against the side and then allowing it to drain, showed the difference to be about 4-5%.

The yields of p-nitroaniline can now be raised to 90-92%.

Acid Anion

The presence of the phosphorus acid anion was shown in one case, that of 1-oxo-1-hydroxy-2,2,3-trimethyl phospha-cyclobutan. The alkaline hydrolysate was acidified and separated using paper chromatography (Whatman No. 1 paper, ether developer). The hydrolysate and authentic acid gave blue spots with a blue tail, R_f = 0.47, the position of the spots being determined by the chromogenic agent of Hanes and Isherwood.[164]

Neopentyl α-methoxyimino-p-nitrobenzyl methylphosphonate

Diazomethane (0.32-0.35 g.) was prepared by the small scale method of Vogel [31e] in ether solution and dried over potassium hydroxide pellets (3 hours). The solution was added to neopentyl α-hydroxyimino-p-nitrobenzyl methylphosphonate (0.5 g.) in dioxan (20 ml.). After five minutes when gas evolution had ceased, the excess of diazomethane was removed with acetic acid. After

removal of dioxan, the residual oil in chloroform was washed with alkali, water, and dried. The p.m.r. spectrum of the resulting yellow oil did not exhibit the NOH proton, but had a new absorption at τ 5.72 (3 protons) and was considered to be neopentyl α-methoxyimino-p-nitrobenzyl methylphosphonate (Found: C, 48.4; H, 6.1. $C_{14}H_{21}N_2O_6P$ requires C, 48.7; H, 6.1%). The p.m.r. spectrum (20% $CDCl_3$ solution) showed absorptions at:- τ 1.91 (quartet, aromatic, 4H); 5.72 (singlet, $NOCH_3$, 3H); 6.20 (octet, $POCH_2$-, 2H); 8.22 (doublet, P-CH_3, 3H) and 9.02 (singlet, Bu^t, 9H) and the i.r. spectrum (liquid film) peaks at: 1638 (ν C=N), 1598 (ν aromatic), 1350 and 1525 (ν NO_2), 1260 (ν P=O), 1035 and 930 (ν $POCH_2$), and 860 $cm.^{-1}$ (δ NO_2Ar).

The behaviour of this methylated compound was examined in acid and alkaline solution. The compound (about 70 m.g.) in dioxan (0.7 ml.) was added to the Radiometer titration cell, which was maintained at pH 2.45 on 'pH stat.' After the initial slight disturbance to the system, a continuous trace with no change was obtained over one hour (this corresponds to 7 half-lives of reaction time of the non-methylated compound).

The alkaline region was examined by u.v. spectroscopy. A drop of the oil in 5% dioxan-water with a drop of sodium hydroxide solution (2M) gave no absorption in the region 350-400 nm. (λ_{max}

p-nitroaniline 382 nm.) after 105 minutes (which corresponds to 10 half-lives of reaction time of the non-methylated compound). A more concentrated solution (x 15) gave no vivid orange coloration with p-dimethylamino benzaldehyde.

Reaction of Propyl α-hydroxyimino-p-nitrobenzyl Methylphosphonate with (a) Cyclohexylamine and (b) Methanol

(a) Cyclohexylamine

Cyclohexylamine (25 ml.) was added to the phosphonate (0.3 g.) in dioxan (5 ml.). After 11 hours at room temperature, the solvents were removed at room temperature under reduced pressure. The addition of petrol (40-60°) to the residue dissolved in the smallest volume of dioxan precipitated a light yellow solid (0.15 g.) A further quantity of the solid (22 m.g., identified by its i.r. spectrum) was obtained by elution with ether of the residue absorbed on alumina. The solid was identified as cyclohexyl p-nitrophenyl urea (79%) by comparison of its i.r. spectrum to that of an authentic sample. The compounds had identical R_f values (alumina, ether solvent, iodine detection, $R_f = 0.36$), m.p. and mixed m.p. 196°, resolidification and second m.p. 236°.

Cyclohexyl p-nitrophenyl urea was made by allowing p-nitrophenyl isocyanate (0.4 g., 2.44 m.moles) in dioxan (10 ml.) to react with cyclohexylamine (0.24 g., 2.44 m.moles) for one hour

and crystallised from methanol, m.p. 196°, resolidification and second m.p. 241° (Found: C, 59.7; H, 6.3. $C_{13}H_{17}N_3O_3$ requires C, 59.3; H, 6.5%). U.v. λ_{max} 333 nm. (ethanol). I.r. (mujol mull) 3380 and 3150 (ν N-H), 1661 (ν C=O), 1550 and 1323 (ν NO_2) and 857 $cm.^{-1}$ (δ NO_2Ar).

(b) Methanol

Methanol (70 ml.) was added to a solution of the phosphonate (270 m.g.) in dioxan (10 ml.) and left to stand for 24 hours at room temperature. After removal of solvents under reduced pressure at room temperature, the addition of ether precipitated a solid (70 m.g.). A p.m.r. spectrum of the solid showed it to be methyl α-hydroxyimino-p-nitrobenzyl methylphosphonate, whose n.m.r. spectrum ($CDCl_3$) showed absorptions at: τ 1.78 (quartet, aromatic, 4H); 6.14 (doublet, $POCH_3$, J_{POMe} 11 Hz, 3H); and 8.23 (doublet, PCH_3, J_{PMe} 18 Hz, 3H).

Additional peaks in the spectrum with proton ratios not related to those of the adduct at τ 8.81 (triplet, 3H) and at 6.5 (quartet, 2H) were assigned to ether. There were no absorptions attributable to the propyl ester moiety.

Determination of the pK_a of α-Hydroxyimino-p-nitrobenzyl Diethylphosphinate

This compound cannot undergo acid hydrolysis and the pK_a was

determined by Radiometer titration of the adduct in 3.5% ethanol -dioxan water of ionic strength μ=0.1, following the method of Albert and Sergeant.[165] The mean pK_a value was 4.65 ± 0.10 at 25.00°.

Hydrolysis of Diethyl α-hydroxyimino-p-nitrobenzyl phosphate

The hydrolysis at low pH was complicated by the two ester groups available for hydrolysis and the greater degree of p-nitroaniline formation. At pH 8-9 and 25.00° the rate of formation of p-nitroaniline was too fast to measure and the increase in the observed rate coefficient from pH 2-4 reflects the greater proportion of p-nitroaniline being formed. At pH 2.50, the solution was visibly coloured yellow.

The hydrolysis of the ester moieties was studied by n.m.r. spectroscopy. A solution of the compound in d-DMSO had the expected spectrum of the adduct: τ 1.80 (quartet, aromatic, 4H); τ 5.78 (quintet, $POC\underline{H}_2CH_3$, 4H) and τ 8.79 (triplet, $POCH_2C\underline{H}_3$, 6H).

Rapid hydrolysis (pseudo-unimolecular) occurred on the addition of D_2O to form a 20% aqueous solution. The p.m.r. signals due to the ester moiety at τ 5.8 declined, with increasing signal strength of the methylene protons of free ethanol at τ 6.5. The first ester moiety was completely lost after 10 minutes (half-life, therefore, about 1 minute at 35.5°), while the second

ester moiety was only 75% hydrolysed after a further $1\frac{1}{2}$ hours.

The p.m.r. spectrum of the final solution (after 15 hours showed that complete hydrolysis had occurred, showing absorptions at: τ 1.81 (quartet, aromatic, 4H); τ 6.50 (quartet, $CH_3\underline{CH_2}OH$, 4H); and τ 8.90 (triplet, $\underline{CH_3}CH_2OH$, 6H).

The rate constants determined at 25.00° at pH 2-4 refer to the loss of one ester moiety as determined from the volume of titrant added.

Reaction of p-Nitrophenyl isocyanate in Aqueous Alkaline Solution

p-Nitrophenyl isocyanate (0.04 m.moles) in dioxan (0.5 ml.) was added to the Radiometer titration cell at pH 8.48 and 25°. Rapid uptake of sodium hydroxide solution occurred, which was completed in 2 minutes to give a yellow solution, λ_{max} 385 nm. (λ_{max} p-nitroaniline, 382 nm.). The rate of addition of sodium hydroxide was limited by the rate of operation of the automatic burette and it is thus considered that p-nitrophenyl isocyanate reacts instantaneously to form p-nitroaniline under the reaction conditions.

Reaction Kinetics

The rates were determined using a Radiometer titration

assembly, a Titrator TTT11, a Titrigraph SBR 2c, and a burette assembly SBU 1a. The 100 ml. capacity titration vessel had a thermostatically controlled jacket. The temperature control at 25.00° was ±0.005° and at other temperatures ±0.1°. Radiometer Type C glass and K401 saturated potassium chloride electrodes were fitted through a lid to the vessel, together with the automatic burette. A stirrer paddle was mounted through the lid and driven externally by an electric motor. The titration vessel was protected by self-indicating sodalime guard-tube.

A stock solution of ionic strength μ=0.1 with [HCl] = 0.01M and [NaCl] = 0.09M was used. During the titration, not more than 0.5 ml. of sodium hydroxide (0.1N) was added. Thus, the ionic strength of the solution was 0.1M ± 0.002M. 25 ml. of the stock solution was brought to the desired pH and allowed to come to equilibrium for $\frac{3}{4}$ hour.

The compound (0.04 m.mole) in dioxan (0.5 ml.) was added via a syringe into the titration vessel. In the acid region, sodium hydroxide solution (0.1M, B.D.H. carbonate free) was added immediately to follow the rate of production of acid. At intermediate and alkaline pH, rapid deprotonation was corrected manually to return the pH to the desired value, and the automatic titrator then allowed to follow the reaction.

The solutions were 2% in dioxan for all of the hydrolyses except for some of the phosphinate adducts, where it was necessary to use a 4% ethanol-dioxan/water mixture because of the reduced solubility (indicated by ‡ in Table 25). It was found, however, that when the reaction medium for some of the phosphonate adducts was changed to 4% aqueous dioxan, or 4% aqueous ethanol-dioxan no change in rate coefficient occurred. As the titration proceeded in alkaline solution, the contents of the Radiometer cell became bright yellow. At low pH, the solution became more yellow as the rate dropped off above pH 3.

Rate constants were calculated either by Guggenheim's method or by the use of the integrated first-order rate equation.

Values of the first-order rate constants are tabulated at low pH at 25.00° (Table 24), high pH at 25.00° (Table 25), and at high pH at varying temperatures (Table 26).

Arrhenius parameters are plotted (Table 27) and values of the energies and entropies of activation are tabulated (Table 28). Values of the entropy of activation were calculated by the equation of Schaleger and Long.[33]

A continuous rate - pH profile was determined only for ethyl α-hydroxyimino-p-nitrobenzyl methylphosphonate. As the rate dropped off with increasing pH, so the colour of the reaction

solution became more intensely yellow. For the adducts capable of acid hydrolysis, the rate was followed to pH 3.5 and in the alkaline region where the values were essentially constant, over the short range of pH 8-9.

The reaction of ethyl α-hydroxyimino-p-nitrobenzyl t-butylphosphonate was slow in acid solution, the first-order rate constant was 4.1×10^{-3} min.$^{-1}$ at pH 2.50. This value represents both hydrolysis to yield ethanol (detected by g.l.c., 15% D.N.P., 60°, Aerograph 1520 B) and rearrangement to yield p-nitroaniline. The u.v. spectrum of the hydrolysate showed the presence of p-nitroaniline (λ_{max} 380 nm.) and of the 1:1 adduct or its hydrolysis product (λ_{max} 268 nm.).

TABLE 24: Rate Constants (25.00°) for Acidic Hydrolysis of (RO)R'P(O)OC(p-$NO_2C_6H_4$)=NOH

R	R'		pH and Rate Constants ($10k_1$ min.$^{-1}$)					
Me	Me	pH	2.10	2.39	2.75	3.09		
		$10k_1$	3.56	6.10	8.7	18.1		
Et	Me	pH	2.10	2.50	2.80	3.00	3.28	3.50
		$10k_1$	6.90	7.00	7.10	7.10	7.50	6.50
		pH	3.72	4.00	4.32	4.50	4.63	5.02
		$10k_1$	5.90	5.30	3.40	4.20	2.60	2.30
		pH	6.00	6.58	6.80			
		$10k_1$	1.50	1.30	1.20			

(TABLE 24, contd.)

R	R'		pH and Rate Constants ($10k_1 min.^{-1}$)					
Pr	Me	pH	2.00	2.32	2.67	3.00	3.31	3.60
		$10k_1$	4.73	4.69	4.60	3.84	3.96	3.50
Pr^i	Me	pH	2.08	2.40	2.89	3.15	3.35	3.60
		$10k_1$	1.37	1.46	1.47	1.45	1.41	1.21
		pH	3.90					
		$10k_1$	1.01					
$Bu^t.CH_2$	Me	pH	2.00	2.35	2.58	3.00	3.32	3.61
		$10k_1$	0.87	0.85	1.03	1.00	0.84	0.85
		pH	3.99					
		$10k_1$	0.62					
$Bu^t.CHMe$	Me	pH	2.10	2.40	2.72	3.00	3.24	3.52
		$10k_1$	0.09	0.10	0.10	0.11	0.12	0.13
Et	Et	pH	2.19	2.30	2.60	2.89	3.19	3.32
		$10k_1$	2.60	2.90	4.20	4.00	3.90	3.30
		pH	3.60					
		$10k_1$	2.90					
Et*	Ph	pH	2.11	2.53	2.63	2.71	2.83	2.91
		$10k_1$	0.54	1.11	1.52	2.00	2.23	1.88
		pH	3.10	3.31	3.53			
		$10k_1$	1.67	1.54	1.37			
Et	Bu^t		very slow at pH 2.5					

(TABLE 24, contd.)

R	R'		pH and Rate Constants ($10k_1 min.^{-1}$)					
Me*	Me	pH	2.31	2.40	2.46	2.50	2.54	2.59
		$10k_1$	2.11	2.17	2.38	2.55	2.67	3.04
		pH	2.66	2.73	2.80	2.90	2.94	3.00
		$10k_1$	3.21	3.27	3.15	2.94	3.00	2.89
		pH	3.16	3.42	3.62			
		$10k_1$	2.70	2.28	2.34			

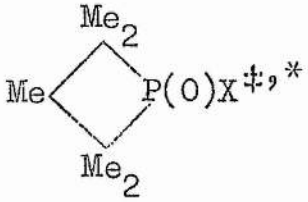
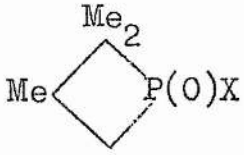
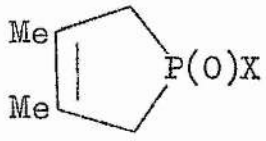
*At 0.00°.

All of the rate coefficients for both acid and alkaline solution hydrolysis are estimated to have an accuracy of ± 4%. The values of the activation energies are accurate to ± 5% and the entropies of activation to ±1 e.u. (Table 28).

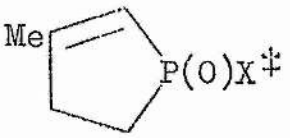
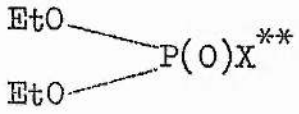
TABLE 25: Rate Constants (25.00°) for Alkaline Hydrolysis of $RR'P(O)OC(p\text{-}NO_2C_6H_4)=NOH$

R	R'	pH and Rate Constants ($10k_1 min.^{-1}$)			
MeO	Me	pH	7.95	8.42	9.07
		$10k_1$	1.10	1.05	1.03
EtO	Me	pH	8.00	8.60	9.09
		$10k_1$	0.90	0.88	0.82
PrO	Me	pH	7.98	8.48	8.95
		$10k_1$	0.74	0.72	0.67
Pr^iO	Me	pH	8.09	8.48	9.10
		$10k_1$	0.45	0.47	0.44

(TABLE 25, contd.)

R	R'	pH and Rate Constants ($10k_1 min.^{-1}$)			
$Bu^t.CH_2O$	Me	pH	8.03	8.50	9.05
		$10k_1$	0.60	0.61	0.59
$Bu^i.CHMeO$	Me	pH	8.00	8.48	8.95
		$10k_1$	0.41	0.40	0.41
EtO	Et	pH	7.98	8.48	9.04
		$10k_1$	0.78	0.66	0.67
EtO	Bu^t	pH	8.04	8.47	9.08
		$10k_1$	0.65	0.59	0.57
EtO	Ph	pH	7.97	8.48	8.97
		$10k_1$	3.70	4.42	4.79
Et	$Et^{\ddagger}$	pH	7.87	8.47	8.98
		$10k_1$	0.096	0.064	0.042
Adduct					
		pH	7.95	8.45	9.08
		$10k_1$	0.59	0.54	0.47
		pH	8.05	8.45	9.30
		$10k_1$	0.36	0.39	0.37
		pH	7.98	8.53	9.09
		$10k_1$	0.17	0.14	0.14

(TABLE 25, contd.)

Adduct	pH and Rate Constants ($10k_1$ min.$^{-1}$)			
	pH	7.98	8.48	9.13
	$10k_1$	0.34	0.29	0.27
	pH	7.91	8.48	8.98
	$10k_1$	0.25	0.27	0.30

*X = $-OC(p\text{-}O_2NC_6H_4)=NOH$.

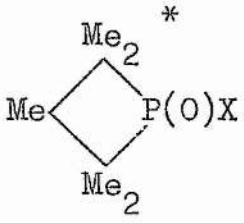
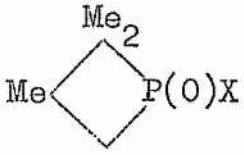
**At 0.0°. Extrapolated value of k_1 at 25.0°, pH 8.48, is 0.91 min.$^{-1}$

‡ 4% dioxan-ethanol: see text.

TABLE 26: Rate Constants at Different Temperatures at pH 8.45 for Hydrolysis of $RR'P(O)OC(p\text{-}NO_2C_6H_4)=NOH$

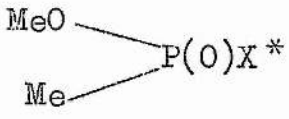
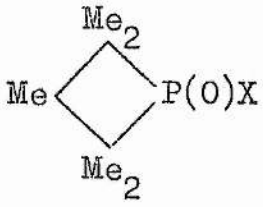
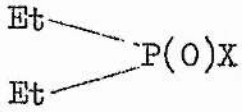
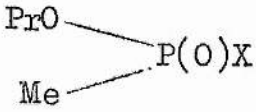
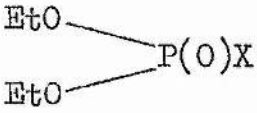
R	R'	Temperature and Rate Constants ($100k_1$ min.$^{-1}$)				
EtO	Bu^t	Temp.	30.7°	25.0	20.3	14.7
		$100\ k_1$	12.0	6.1	3.20	1.60
			12.1	6.0	3.25	1.65
MeO	Me	Temp.	25.0°	18.3	13.9	0.00
		$100k_1$	10.5	4.36	1.99	0.38
EtO	EtO	Temp.	15.8°	12.1	5.0	3.1
		$100\ k_1$	28.2	16.9	5.8	3.10
			27.4	16.5	5.6	3.00
Et	Et	Temp.	39.0°	35.1	29.5	25.0
		$100\ k_1$	2.40	1.72	0.93	0.55
				1.69		0.60

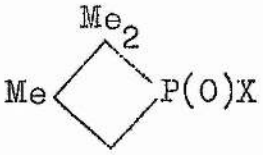
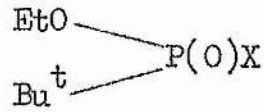
(TABLE 26, contd.)

R	R'	Temperature and Rate Constants ($100\ k_1$ $min.^{-1}$)					
PrO	Me	Temp.	25.0°	19.9	13.9	7.5	
		$100\ k_1$	7.20	4.05	1.70	0.69	
			7.20	4.10		0.66	
EtO	Et	Temp.	25.0°	20.1	13.2	5.7	0.00
		$100\ k_1$	6.5	3.50	1.26	0.60	0.20
			6.4	3.44	1.27	0.54	0.28
		Temp.	31.4°	25.0	20.2	13.4	8.2
		$100\ k_1$	10.4	5.40	2.81	1.32	0.62
			10.8	5.40	2.86	1.29	0.64
		Temp.	25.0°	18.5	18.1	11.7	8.4	2.1
		$100\ k_1$	3.66	1.56	1.53	0.73	0.39	0.23

*X = $-OC(\underline{p}\text{-}O_2NC_6H_4)=NOH$

TABLE 27: Alkaline Rate Constants at Different Temperatures Presented for Arrhenius Plots

	Temp.°C	Temp.°A	$T^{-1}\ 10^{-2}$	k_1 (min.$^{-1}$)	$\log_e 10^3 k_1$
	25.0	298.0	0.3356	0.103	4.6348
	18.3	291.3	0.3433	0.0436	3.7751
	13.9	286.9	0.3508	0.0199	2.9907
	0.0	273.0	0.3663	0.0038	1.3350
	31.4	286.4	0.3285	0.106	4.6635
	25.0	298.0	0.3356	0.054	3.9890
	20.2	293.2	0.3411	0.028	3.3429
	13.4	286.4	0.3492	0.013	2.5726
	8.2	281.2	0.3557	0.0063	1.8405
	39.0	312.0	0.3205	0.024	3.1781
	35.1	308.1	0.3246	0.017	2.8332
	29.5	302.5	0.3306	0.0093	2.2300
	25.0	298.0	0.3356	0.0058	1.7579
	25.0	298.0	0.3356	0.072	4.2767
	19.9	292.9	0.3415	0.041	3.7136
	13.9	286.9	0.3486	0.017	2.8332
	7.5	280.5	0.3577	0.0068	1.9168
	15.8	288.8	0.3462	0.278	5.6277
	12.1	285.1	0.3508	0.167	5.1180
	5.0	278.0	0.3597	0.058	4.0605
	0.0	273.0	0.3663	0.0305	3.4177

	Temp.°C	Temp.°A	$T^{-1}10^{-2}$	k_1 (min.$^{-1}$)	$\log_e 10^3 k_1$
	25.0	298.0	0.3356	0.0366	3.6001
	18.5	291.5	0.3431	0.0156	2.7473
	18.1	291.1	0.3435	0.0153	2.7279
	11.7	284.7	0.3512	0.0073	1.9879
	2.1	275.1	0.3635	0.0023	0.8329
	25.0	298.0	0.3356	0.0645	4.1667
	20.1	293.1	0.3412	0.0347	3.5468
	13.2	286.2	0.3495	0.0127	2.5616
	5.7	278.7	0.3601	0.0057	1.7405
	0.0	273.0	0.3663	0.0028	1.0296
	30.7	303.7	0.3293	0.120	2.4849
	25.0	298.0	0.3356	0.061	1.8083
	20.3	293.3	0.3410	0.032	1.1910
	14.7	287.7	0.3475	0.0163	0.4886

*X = $-OC(\underline{p}\text{-}O_2NC_6H_4)=NOH$

Good Arrhenius plots resulted for all the compounds. The plot for ethyl α-hydroxyimino-p-nitrobenzyl t-butylphosphonate is typical of those obtained.

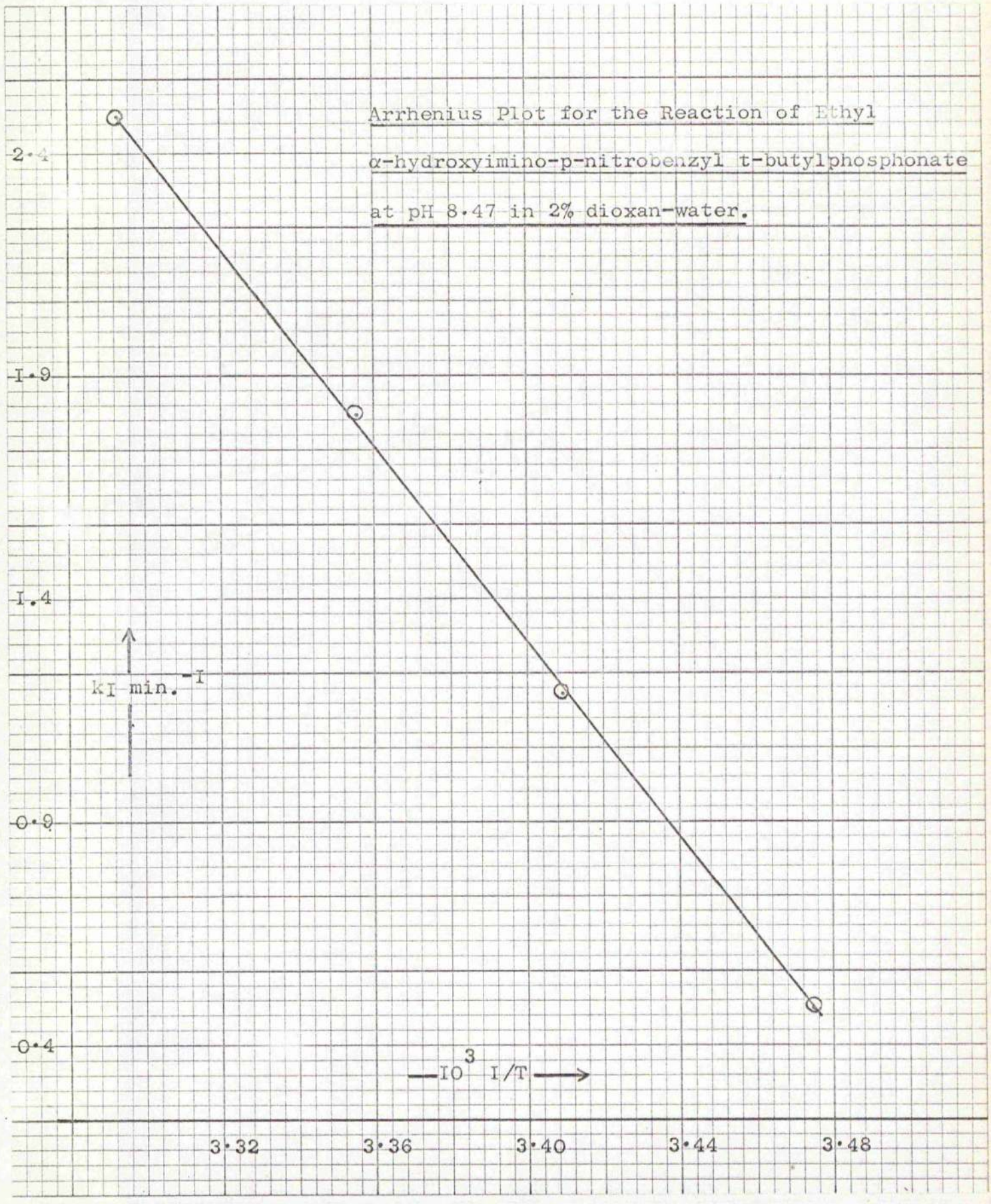
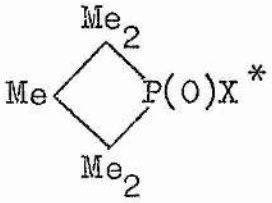
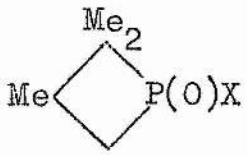

Arrhenius Plot for the Reaction of Ethyl
α-hydroxyimino-p-nitrobenzyl t-butylphosphonate
at pH 8.47 in 2% dioxan-water.
2·4
1·9
1·4
0·9
0·4
k1 min.⁻¹
—IO³ I/T →
3·32
3·36
3·40
3·44
3·48

TABLE 28: Arrhenius Parameters for the Alkaline Hydrolyses of $RR'P(O)OC(p\text{-}NO_2C_6H_4)=NOH$

R	R'	Temp. Range	pH	E_{act} (Kcals/mole)	$\Delta S^{\ddagger}$ (eu.)
EtO	EtO	3-16°	8.45	22.2	+7.3
EtO	Et	0-25	8.48	18.7	-11.4
Et	Et	25-39	8.48	18.7	-16.2
MeO	Me	0-25	8.44	19.5	-7.8
EtO	Bu^t	15-30	8.47	22.3	+0.5
PrO	Me	8-25	8.48	21.1	-3.2
		8-31	8.45	19.6	-8.8
		2-25	8.48	20.7	-4.7

*X = $-OC(p\text{-}NO_2C_6H_4)=NOH$

Hydrolysis of Ethyl Pinacolyl Methylphosphonate

Reagents

Ethyl pinacolyl methylphosphonate was prepared by the method of Cadogan[143] and had b.p. 52/0.4 mm.; n_D^{24}, 1.4230.

Benzenesulphonic acid was supplied as a 30% solution and the p-toluenesulphonic acid was of B.D.H. M.A.R. qualtty.

G.l.c. Analysis

Analysis of the olefins formed during the hydrolysis was performed on a 7' column of 15% dinonyl phthalate absorbed on silocel at 23°, using an Aerograph 1520B chromatograph equipped with a flame ionization detector.

Kinetic Measurements

The rate of acid hydrolysis was followed in sealed tubes immersed in an oil bath at 100° ± 0.02°. 2 ml. of a solution of known concentration of the ester in ethanol and 2 ml. of aqueous p-toluenesulphonic acid (1.86M) were sealed into each tube and, after incubation and cooling, the contents of the tube were titrated against standard alkali using bromophenol blue as indicator.

The rate of hydrolysis was also followed by the rate of formation of the olefins. A known volume of standard bromate solution with excess bromide ion was added to the tube and the excess of

bromine titrated as the quantity of iodine liberated by added iodide ion using standard sodium thiosulphate solution and starch indicator. A blank run of ethanol and p-toluenesulphonic acid showed that no unsaturated material was formed at 100° for 13 hours.

Infinity values were calculated from the amount of ester taken. First-order rate constants were obtained graphically using the integrated first-order rate equation (Table 29).

TABLE 29: First-order Rate Constants for Hydrolysis of Ethyl Pinacolyl Methylphosphonate in 50% aqueous-ethanol, 0.93M with respect to p-Toluenesulphonic acid, at 100°

Acid titration	$10^3 k_1$ (min.$^{-1}$)	2.38	2.45
Olefin titration	$10^3 k_1$ (min.$^{-1}$)	0.67	0.68

Under similar reaction conditions, the rate constant for the dehydration of pinacolyl alcohol was estimated to be 8.7×10^{-5} mins.$^{-1}$ A blank experiment in which known weights of the olefins were kept under the reaction conditions for 5 hours and then titrated, showed a discrepancy of about 70% which was attributed to the volatility of, and to possible hydration of, the olefins in

the reaction mixture.

A g.l.c. technique was also employed to follow the concentration of olefins in the reaction mixture. The ester in 1N benzenesulphonic acid in aqueous dioxan (50% v/v, 4 ml.) was heated in a sealed tube at 100° for 13.8 hours. When cool, a portion (2 ml.) was added to dry, ethanol-free chloroform (5 ml.) in a cooled separating funnel. The mixture of olefins so extracted into the chloroform layer was analysed by g.l.c. using the 15% DNP column. Calibration of the procedure with known mixtures of the authentic olefins indicated a precision of ± 20-30%.

Dehydration of pinacolyl alcohol to give the same mixture of olefins was conducted under similar conditions (100° for 47 hours). The results of these experiments (Table 30) again show that the dehydration of the alcohol is a slower process than the formation of the olefins from ethyl pinacolyl methylphosphonate.

The semi-quantative results, assuming a first-order reaction, lead to a rate constant (k_1) of 0.9×10^{-3} min.$^{-1}$, which compares with the $k_1 = 3.7 \times 10^{-3}$ min.$^{-1}$ determined by the more accurate titrimetric method.[135] The corresponding k_1 for dehydration of pinacolyl alcohol is 3.5×10^{-5} min.$^{-1}$

TABLE 30: Production of Olefins by the Hydrolysis of Ethyl Pinacolyl Methylphosphonate and the Dehydration of Pinacolyl Alcohol in Acidic Solution at 100°

Ester (moles x 10^4)	Alcohol (moles x 10^4)	Olefin (% moles)	Ratios of Isomeric Olefins		
			$Bu^tCH{:}CH_2$	$Me_2CH{\cdot}CMe{:}CH_2$	$Me_2C{:}CMe_2$
8.04		24	1	21	104
8.13		39	1	34	173
10.60		35	1	11	100
	3.95	8	1	25	113
	3.81	10	1	23	104

Product Analysis of Hydrolysis

A g.l.c. examination of the hydrolysis products of the pinacolyl ester after 6.5 hours at 100° showed the presence of the three olefins expected to be derived from the pinacolyl carbonium ion. They were identified by comparison with the authentic olefins, which were kindly supplied by the B.P. Research Centre, Sunbury-on-Thames. The olefins gave well-separated peaks at 23° (retention time in brackets):- 3,3-dimethylbut-1-ene (1.5 mins.), 2,3-dimethylbut-1-ene (2.5 mins.), and 2,3-dimethylbut-2-ene (4.7 mins.).

Extraction of the aqueous solution with chloroform yielded a small quantity of a gummy oil, which was distilled to give a

colourless oil, whose n.m.r. and i.r. spectra were identical to authentic ethyl hydrogen methylphosphonate.

The Intermediacy of Pinacolyl Alcohol during the Hydrolysis

It was found to be just possible to detect 1.5×10^{-9} moles of pinacolyl alcohol on a 10% CAR 20M column at 25° using a Perkin-Elmer F11 chromatograph.

The ester (0.8665 g., 41.6 m.moles) was added to 50% aqueous dioxan (5 ml.) 1M with respect to benzenesulphonic acid, and heated at 100° for 6.8 hours. After quenching the mixture, it was then extracted with chloroform (10 ml.) and examined by g.l.c. No peak due to pinacolyl alcohol was observed, and it was estimated that the hydrolysis mixture did not contain more than 6.1×10^{-5} moles of the alcohol. The combined rate equation for two consecutive first-order reactions, the hydrolysis to give pinacolyl alcohol followed by dehydration of the liberated alcohol, using the g.l.c. determined rate constants, showed that the limit of detection of pinacolyl alcohol was less than 1% of that theoretically possible in the hydrolysis.

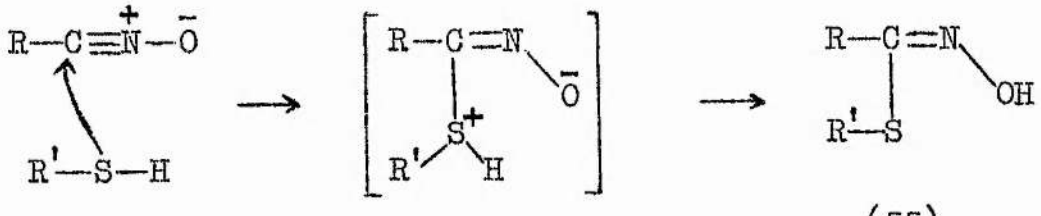
A separate experiment showed that the extraction of pinacolyl alcohol from acid aqueous dioxan by chloroform was quantative.

DISCUSSION

The chemistry of nitrile oxides has been reviewed by Grundmann.[142] In general, unless sterically prevented, nitrile oxides are very labile towards auto-condensation. All simple aliphatic, and most aromatic and heterocyclic nitrile oxides are stable only at temperatures below -70°. p-Nitrobenzonitrile oxide is unique in that it is reported[142] to be stable for longer than thirty days. The most frequently observed mode of auto-condensation of nitrile oxides is their dimerization to furoxans (1,2,5-oxadiazole-2-oxides). This is the normal reaction of nitrile oxides in solution or under storage, at room temperature and neutral conditions.

Nitrile oxides undergo a variety of addition reactions with proton donors, hydrogen halides, thiols, phenols, and amines. The reaction of water with a nitrile oxide to give a hydroxamic acid is reported to be acid-catalysed.[166]

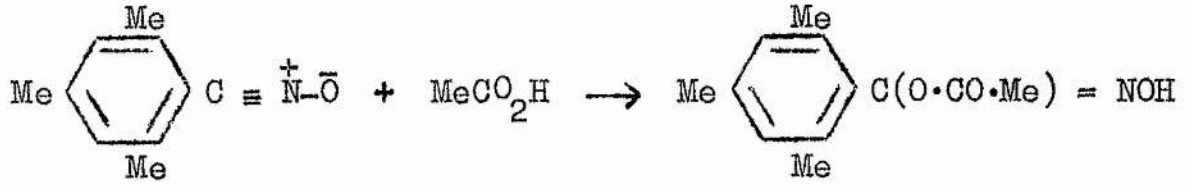
Thiols add easily to aromatic nitrile oxides to yield alkyl thiohydroximic acids (55). Benn[140] proposed that the cis isomer of the adduct was formed. This is supported by the use of this route for the synthesis of naturally occurring mustard oil



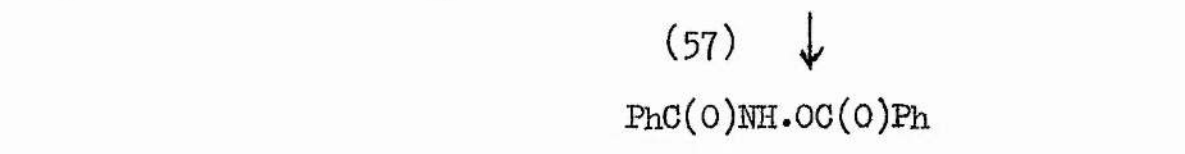
(55)

glucosides, which are alkyl thiohydroximic acid derivatives and have been proved by X-ray crystallography to possess the cis configuration.[167]

Adducts of nitrile oxides with carboxylic acids[166] and their silver salts[168] have been described. Grundmann and Frommeld[166] reported the formation of the adduct (56). A similar product (57) had previously been shown to rearrange readily.[168]



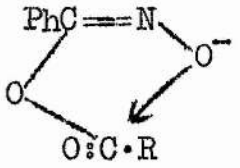
(56)



(57)

PhC(O)NH.OC(O)Ph

Alexandrou and Nicolaides[169] studied the reaction of benzonitrile oxide and the salts of carboxylic acids. They isolated not the initial addition product (analogous to 56), but the rearranged product (58) similar to that obtained by Werner.[168] The aryl benzamide (58) was suggested to have arisen from an intramolecular acyl migration thus:

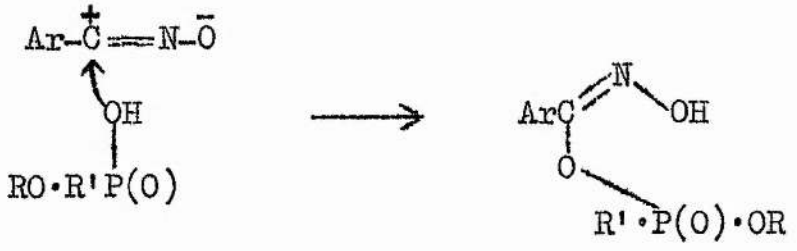


$\longrightarrow$ Ph·C(O)NH·OC(O)R

(58)

During the present work, a number of adducts ArC(Y) = NOH have been prepared from p-nitrobenzonitrile oxide and phosphorus acids, where Y is a phosphorus acid anion and Ar is p-nitrophenyl. (In all subsequent formulae, Ar will always represent the p-nitrophenyl moiety.) The formation of the adduct of p-nitrobenzonitrile oxide with the phosphorus acid was always accompanied by varying quantities of the dimerization product of p-nitrobenzonitrile oxide, p-nitrophenyl furoxan. The two compounds were easily separated, however, by the solubility of the 1:1 adduct with the phosphorus acid and the insolubility of the dimer, p-nitrophenyl furoxan, in alcohols.

By analogy with the addition of thiols and the rapid rearrangement of Alexandrou and Nicolaides' adducts, which would be expected to proceed via the cis form in the intramolecular acyl migration, the addition of the phosphorus acid probably occurs to give the cis isomer (59) thus:



(59)

This form will also be expected to be stabilised by intramolecular hydrogen bonding.[96]

The suggested structures of the adducts were in accord with the p.m.r. and i.r., spectra obtained for them. The compounds were instantaneously decomposed by water, and for this reason greater tolerance was allowed with the elemental analysis. The adducts prepared are summarised in Tables 19 and 21 (pages 138 and 143 respectively). The rate constants for their solvolytic behaviour are to be found in Tables 24, 25, and 26 (pages 160, 162, and 164 respectively).

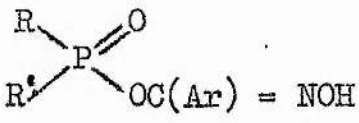
The position of the infra-red oxime stretching frequency is interesting because of the two positions observed for it. The alkyl methylphosphonate adducts (59; R' = Me) showed values at about 1630 $cm.^{-1}$, while all the other adducts showed values at about 1700 $cm.^{-1}$ Bellamy[39] quotes the ν C = N absorption in open-chain or in non-conjugated ring systems as lying within the range 1690-1640 $cm.^{-1}$ There appears to be no simple explanation of the two absorption values observed.

Cadogan and Maynard[139,170] reported the adduct ethyl α-hydroxyimino-p-nitrobenzyl methylphosphonate (59; R = Et, R' = Me) to be light sensitive. As a result all of the adducts reported in this thesis were prepared and stored under dark

conditions. However, dioxan solutions of the adducts were stable for at least a day in moisture-protected vessels, which were not maintained in darkness.

Nomenclature

The adducts of p-nitrobenzonitrile oxide with various dialkyl hydrogen phosphates, alkyl hydrogen alkylphosphonates, and hydrogen dialkylphosphinates including cyclic products have the general formula (60), i.e. alkyl α-hydroxyimino-p-nitrobenzyl alkylphosphyls:



(60)

The adduct from the nitrile oxide and dialkyl hydrogen phosphate will be referred to as the dialkyl phosphate adduct (60; R = R' = alkoxy), and in a similar way the adducts derived from alkyl hydrogen alkylphosphonates and hydrogen dialkylphosphinates will be referred to as the alkyl alkylphosphonate adducts (60; R = alkoxy) and as the dialkylphosphinate adducts (60) respectively.

Solvolytic Behaviour

The three classes of compound, the dialkyl phosphate adduct

(60; R = R' = alkoxy), the alkyl alkylphosphonate adducts (60; R = alkoxy) and the dialkylphosphinate adducts (60) exhibited varying behaviour on hydrolysis at various pH. The results of these hydrolyses are summarised in Tables 24 (acid hydrolysis) and 25 (alkaline hydrolysis), pages 160 and 162, respectively. In acid solution a very fast hydrolysis occurred, with the loss of the ester moiety (Table 22, page 148). In alkaline solution migration of the phosphyl anion took place similar to that reported by Alexandrou and Nicolaides,[169] but in the present work with further reaction to yield p-nitroaniline.

The kinetics of the hydrolysis of the adducts (60) were studied over the range pH 2-4 and the phosphyl migration at pH 8-9 (Figures 1 and 2, pages 182 and 183 respectively). In one case, that of ethyl α-hydroxyimino-p-nitrobenzyl methylphosphonate (60; R = OEt, R' = Me), it was shown that the observed rate constants fell on a smooth curve over the range pH 2-9 (Figure 1, page 182). The intensity of the yellow colour in the hydrolysate grew with increasing pH, and this was taken to indicate the gradual change-over in route from hydrolysis of the ester moiety in acid solution pH 2-3·5, to the formation of p-nitroaniline in solutions with pH > 7.

In only two cases, that of the diethyl phosphate adduct (60; R = R' = OEt) and the ethyl t-butylphosphonate adduct (60;

R = OEt, R = Bu^t), was the rate of alkaline hydrolysis forming p-nitroaniline greater than the rate of hydrolysis of the alkyl ester moiety. The observed rate constants for the diethyl phosphate adduct (60; R = R' = OEt) thus rose at pH >3, rather than falling as for the other adducts (60).

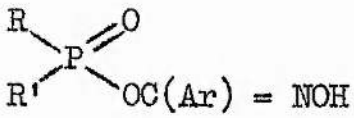
The observed rate constants fell as the pH was increased above 3 (Figures 1 and 2, pages 182 and 183). The Radiometer titration curve showed a very rapid initial uptake of alkali, followed by the usual first-order hydrolysis. The adjustment of the pH of an alkaline solution of the ethyl methylphosphonate adduct (60; R = EtO, R' = Me) to an acid solution resulted in the usual acid hydrolysis of the ester to yield ethanol with a rate constant of k_1, 0·68 $min.^{-1}$ at pH 3 and 25·0°.

It is to be concluded that the initial rapid uptake of alkali, together with the steady decrease in observed rate constant with increasing pH, was due to the reversible ionization of the NOH moiety, thus reducing the concentration of the protonated species. This occurred at a much lower pH than would be expected for the related p-nitrobenzaldoxime, which has a pk_a of 10. Thus, the phosphyl substituent must have a large perturbing effect on the acidity of the oxime. This is verified by the measured pk_a of 4·65 for the diethylphosphinate adduct (60; R' = R = Et) in 3·5% ethanol/dioxan-water.

Hydrolysis in Acid Solution

Values of the rate constants are summarised in Table 24 (page 160) and in Figures 1 and 2 (pages 182 and 183).

The dialkylphosphinate adducts (60) were stable in acid solution. No change was detected by the Radiometer assembly during one hour. The alkyl alkylphosphonate adducts (60; R = alkoxy) and the diethyl phosphate adduct (60; R = R' = OEt) were hydrolysed to yield an alcohol, ROH, and a solid acid derivative (61). The kinetics of hydrolysis obeyed the first-order rate equation. The hydrolyses were performed with a large excess of water, conditions under which a bimolecular reaction involving water would give rise to pseudo-unimolecular kinetics.



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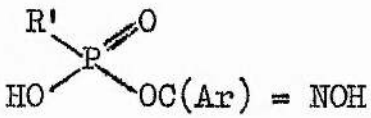


(61)

The most remarkable feature of the hydrolyses is the large enhancement of rate compared with a simple phosphonate, ethyl p-nitrophenyl methylphosphonate. It is well established [50] that simple phosphonates hydrolyse with phosphorus-oxygen fission in alkaline solution, and with carbon-oxygen fission in acid solution.

Hudson and Keay [61] have reported the bimolecular rate

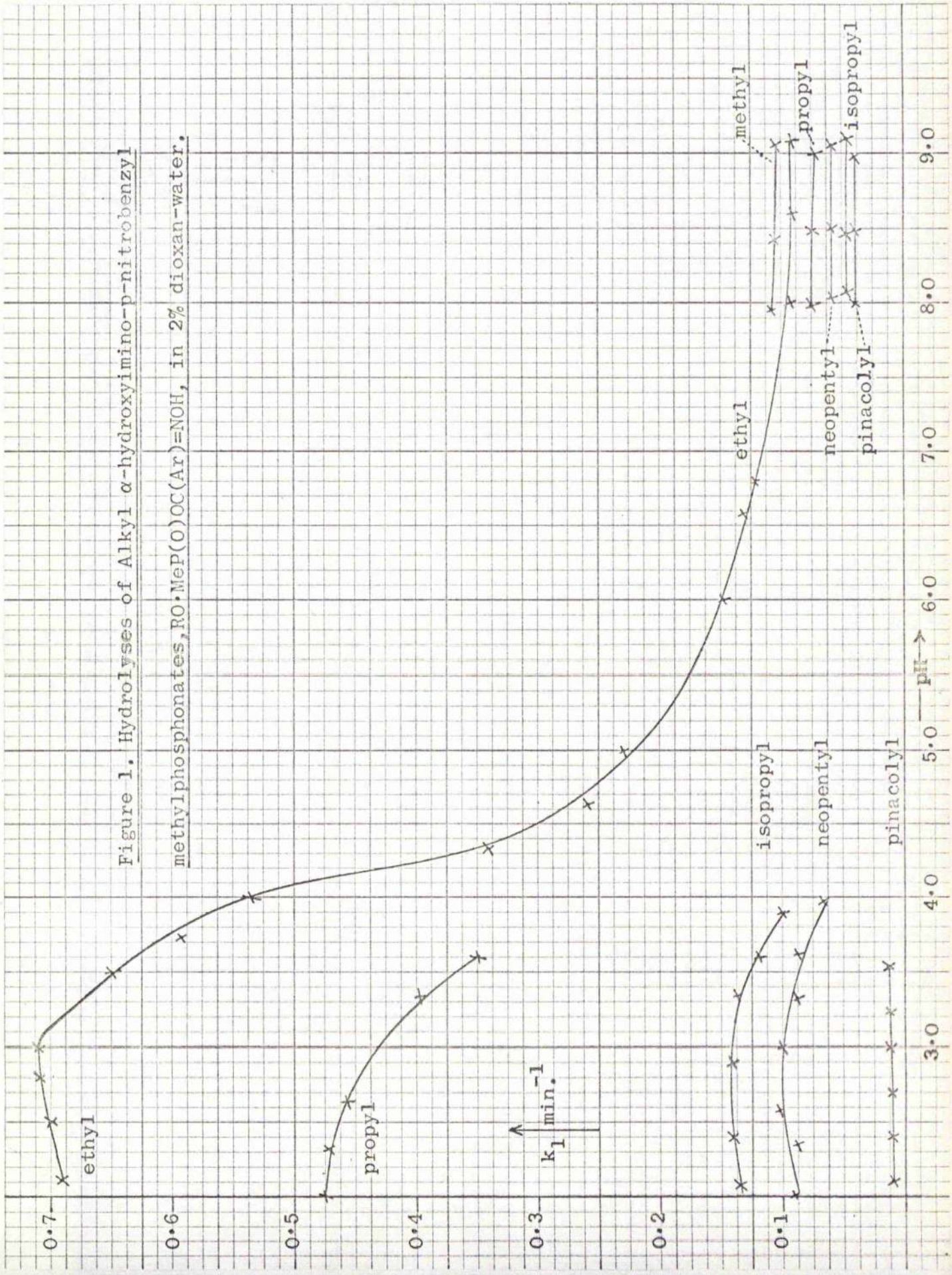
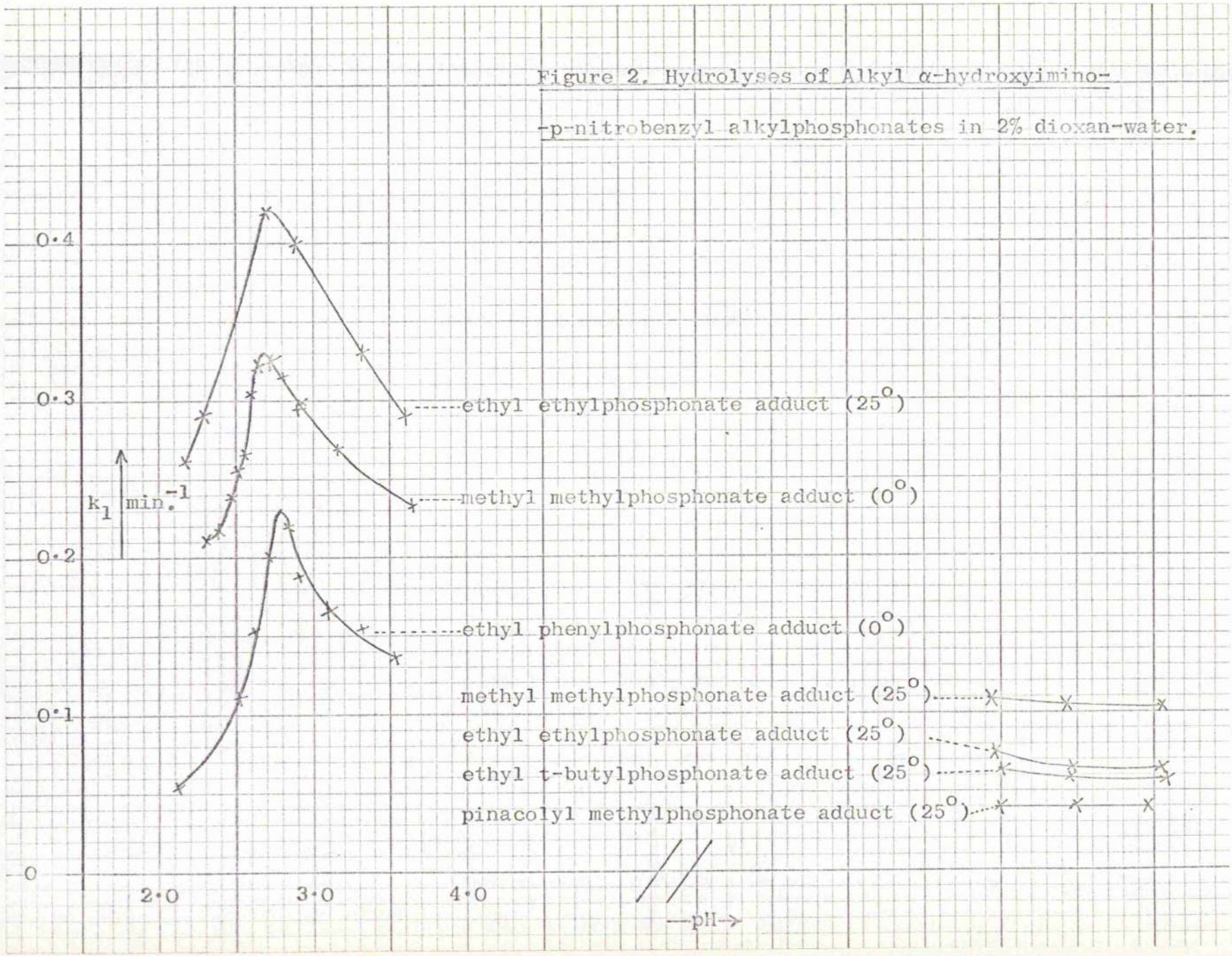


Figure 1. Hydrolyses of Alkyl α-hydroxyimino-p-nitrobenzyl
methylphosphonates, RO·MeP(O)OC(Ar)=NOH, in 2% dioxan-water.
0·7
0·6
0·5
0·4
0·3
0·2
0·1
k_1 min.$^{-1}$
ethyl
propyl
isopropyl
neopentyl
pinacolyl
methyl
ethyl
propyl
isopropyl
neopentyl
pinacolyl
3·0
4·0
5·0
6·0
7·0
8·0
9·0
pH

Figure 2. Hydrolyses of Alkyl α-hydroxyimino-
-p-nitrobenzyl alkylphosphonates in 2% dioxan-water.



constant for the acid-catalysed hydrolysis of ethyl p-nitrophenyl methylphosphonate to give ethanol as 0·055 $l.mole^{-1}min.^{-1}$ at 110°. Maynard[170] has given the relationship between the rate coefficient and absolute temperature for the hydrolysis of the ethyl methylphosphonate adduct (60; R = OEt, R' = Me) as:

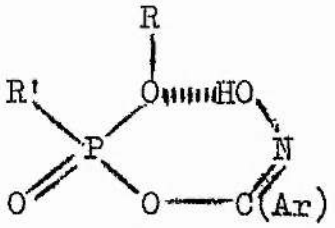
$$\log_{10}k_1 = -3{\cdot}247 \times 10^3T^{-1} + 10{\cdot}378.$$

At pH 2, the rate enhancement of the adduct hydrolysis over that of the simple phosphonate is about 2×10^7. It is important to point out that in the former, hydrolysis occurs at the phosphorus centre and for the latter, with carbon-oxygen fission.

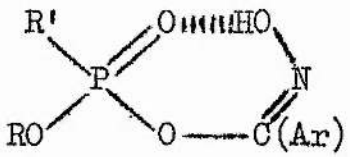
The rate enhancement strongly suggests an intramolecular acceleration involving neighbouring group participation by the fully protonated oxime. This is confirmed by the lack of hydrolysis during seven half-life times (half-life time for the hydrolysis of the non-methylated compound) of neopentyl α-methoxyimino-p-nitrobenzyl methylphosphonate, $Bu^t{\cdot}CH_2O{\cdot}MeP(O){\cdot}OC(Ar) = NOMe$, where the oxime moiety was methylated.

The observed constancy of the rate in the range pH 2-3·5 (Figure 1, page 182) suggests intramolecular catalysis involving the protonated form of the oxime (i.e., = NOH rather than = NO^- or NOH_2^+), and that further protonation of (60) is not necessary. There are two possible transition states involving protonation by

the oxime function, (62) and (63). Protonation on the phosphoryl



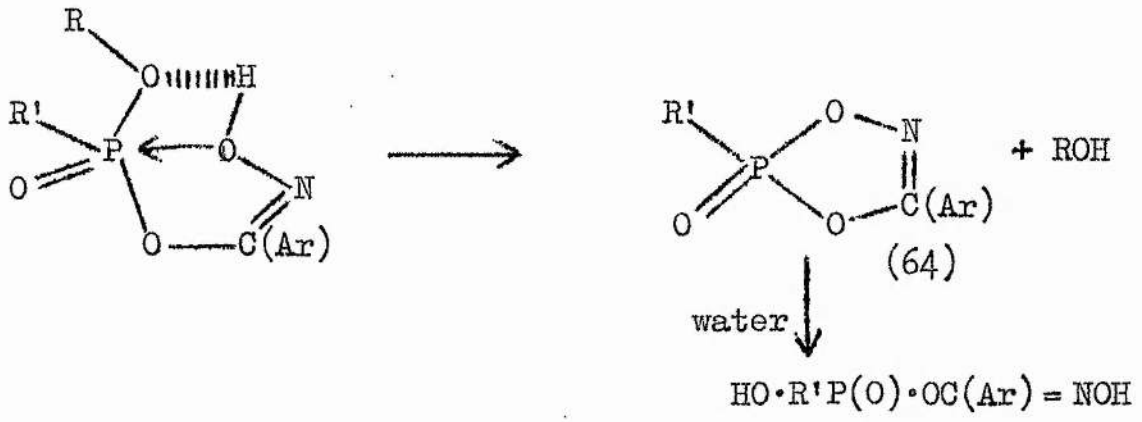
(62)



(63)

oxygen (63) can be discounted as it might be anticipated that the better leaving group would be eliminated to yield a hydroxamic acid (cf. hydrolysis in the alkaline region, where attack by the oximate anion causes elimination of the hydroxamic acid species, rather than the alkoxyl ion). The loss of the ester moiety in acid solution thus indicates protonation of type (62).

The protonated species (62) can decompose by: (a) unimolecular loss of the ester moiety; (b) bimolecular reaction at phosphorus with water; (c) bimolecular reaction with water at the carbon atom of the ester moiety; or (d) the formation of a cyclic intermediate (64) which would be expected to be readily hydrolysed [98] (Scheme 11). All of these mechanisms are in accord with the observed first-order or pseudo first-order kinetics.



Scheme 11

The experimental evidence to be outlined in the following pages is in accord with route (b) above, a bimolecular displacement of the ester moiety at phosphorus, with phosphorus-oxygen fission.

Thus, the quantative trans-esterification of the propyl methylphosphonate adduct (60; R = OPr, R' = Me) into the methyl methylphosphonate adduct (60; R = OMe, R' = Me) by methanol is explicable only by methanolic attack on phosphorus with phosphorus-oxygen fission. The anchimeric assistance available for the hydrolysis is also manifested in this case, as trans-esterifications are generally very slow.[97]

It is well established that substitutions at phosphorus are sensitive to steric crowding.[61,63,68,130] The hydrolysis of the ethyl t-butylphosphonate adduct (60; R = OEt, R' = Bu^t) should be little changed if attack by the nucleophile occurs on the

carbon atom of the ester moiety, since the steric crowding is removed from the reaction site. A hundred-fold reduction in rate was observed (Table 24, page 160) and such a decrease can only be associated with steric crowding at the reaction centre, i.e. the phosphorus atom. A rate decrease would only be expected for a bimolecular reaction. The unimolecular mechanism for the loss of the ester moiety can now be discarded, since it would be expected to be little influenced by steric crowding.

The slower rate of hydrolysis of the ethyl t-butylphosphonate adduct (60; R = OEt, R' = Bu^t) points to the absence of a cyclic intermediate (64). The alkyl methylphosphonate adducts (60; R = alkoxy, R' = Me) have different rates of hydrolysis (Figure 1, page 182) so in the event of intramolecular attack by the oxime, where a common intermediate is formed, the ring-forming step must be rate-determining. The hydrolysis of the ethyl t-butylphosphonate adduct (60; R = OEt, R' = Bu^t) is sterically hindered by a factor of 100, but the rate of alkaline rearrangement to yield p-nitroaniline is that (Figure 2, page 183) of the alkyl methylphosphonate adducts (60; R = alkoxy, R' = Me). It will be shown later in this Discussion that the formation of p-nitroaniline arises from the initial intramolecular attack on phosphorus by the deprotonated oxime moiety.

Any formation of the cyclic intermediate (64) has been deduced to be the rate-determining step in the acid hydrolysis of the adducts. There is no hindrance in forming the five-membered intermediate postulated for the reaction sequence in the alkaline region (Figure 2, page 183). Since the acid hydrolysis of the ethyl t-butylphosphonate adduct (60; R = OEt, R' = Bu^t) is slower ($\times 10^{-2}$), the formation of the cyclic intermediate (64) is incompatible with the experimental results.

In the series of alkyl methylphosphonate adducts (60; R = alkoxy, R' = Me), the rate constants fall in the order Me > Et > Pr > Pr^i > $Bu^t.CH_2$ > $Bu^t.CHMe$ (Figure 1, page 182). This order parallels that of the alkaline hydrolysis of simple phosphonates, where phosphorus-oxygen fission is established, and is contrary to the known order of reactivity of simple phosphonates in acid solution of Pr^i > Me > $Bu^t.CH_2$.

This difference in the order of reactivity of the alkyl methylphosphonate adducts (60; R = alkoxy, R' = Me) and that of simple phosphonates in acid solution is unique, and points to a difference in the routes of hydrolysis of the two types of compound.

Carbon-oxygen fission has been established in acid hydrolyses of simple phosphonates and secondary alkyl ester moieties are lost via a carbonium ion mechanism.[135] In this connection, it is

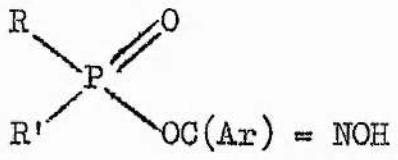
demonstrated in the present work that the acid hydrolysis of ethyl pinacolyl methylphosphonate also proceeds with the formation of the pinacolyl carbonium ion, which eliminates a proton to form three isomeric olefins (see page 172).

Pinacolyl alcohol was formed exclusively from the acid hydrolysis of the pinacolyl methylphosphonate adduct (60; R = OCHMe·Bu^{t}, R' = Me) and this, together with the order of reactivity of the alkyl methylphosphonate adducts (60; R = alkoxy, R' = Me) paralleling that of the alkaline hydrolysis of simple phosphonates, strongly suggests that phosphorus-oxygen rather than carbon-oxygen fission occurs during the acid hydrolysis of the adducts (60).

The experimental results are thus compatible with a bimolecular substitution of water at the phosphorus atom, with protonation of the leaving group by the oxime moiety. Such a bimolecular reaction is compatible with the observed first-order kinetics, since the hydrolyses were performed using an excess of water, conditions which would give rise to pseudo-unimolecular kinetics. Examination of molecular models shows that the leaving group, the phosphorus atom, and the entering water molecule lie in a straight line, and that attack on carbon is sterically difficult.

The alkyl methylphosphonate adducts (60; R = alkoxy, R' = Me)

exhibit slight maxima at about pH 3 in the rate coefficient-pH profile (Figure 1, page 182), before the rate decreases due to increasing intramolecular attack by the oximate moiety. Greater dependence is shown by the ethyl ethylphosphonate adduct (60; R = OEt, R' = Et), the ethyl phenylphosphonate adduct (60; R = OEt, R' = Ph), and the methyl methylphosphonate adduct (60; R = OMe, R' = Me) (Figure 2, page 183). The pseudo-unimolecular rate



(60)

coefficients obtained for these three adducts could not be fitted to any form of second-order kinetics. There is no apparent reason why the methyl methylphosphonate adduct (60; R = OMe, R' = Me) should show such a maximum compared with the remainder of the alkyl methylphosphonate adducts (60; R = alkoxy, R' = Me).

The rates of hydrolysis of the alkyl alkylphosphonate adducts (60; R = alkoxy) are in accord with the known behaviour of simple phosphonate esters. Increasing alkylation at the phosphorus centre in the adducts (60; R = OEt) causes the rate to decrease (Table 32) owing to steric and inductive reasons.[61] The increased rate of reaction of the ethyl phenylphosphonate adduct (60; R = OEt, R' = Ph)

compared with the ethyl methylphosphonate adduct (60; R = OEt, R' = Me) agrees with the findings of Christol and Marty,[63] who studied the alkaline hydrolysis of dimethyl alkylphosphonates. In the Introduction it was suggested that the increased rate of reaction arises from a transition state with relaxed steric requirements due to the planar ring compared with sp^3 hybridised carbon substituted at phosphorus.

A remarkable fact is the way in which the reactivity range of the series of alkyl methylphosphonate adducts (60; R = alkoxy, R' = Me) has been compressed (Table 32), compared with the series of dialkyl methylphosphonate esters. Hudson and Keay,[61] and

Table 32

Relative Rate Constants for Hydrolyses of Alkyl α-hydroxyimino-p-nitrobenzyl alkylphosphonates $RR'P(O)OC(p\text{-}NO_2C_6H_4)=NOH$ at pH 2·75

R' = Me

R	OMe	OEt	OPr	OPr'	$OCH_2 \cdot Bu^t$	$OCHMe \cdot Bu^t$
Rel. Rate	87	71	45	14	10	1

R = OEt

R'	Me	Et	Bu^t
Rel. Rate	71	41	0.4

Christol and Marty[63] reported a much greater reactivity range, encompassing a factor of 1800, for the alkaline hydrolysis of dineopentyl and dimethyl methylphosphonates where comparable phosphorus-oxygen fission occurs. The decrease in reactivity with increasing alkyl substitution in the ester moiety has been suggested to arise from the reduced electrophilicity of phosphorus due to the greater ease of π interactions from oxygen by the inductive effect of the ester alkyl group,[58,63] and increased steric hindrance.[61,63]

In the present work, there is an alternative electron sink, that of the proton derived from the oxime moiety. This interaction between the proton and the oxygen atom of the ester moiety could allow proton to receive part of the π interaction, which would normally participate with the phosphorus atom. Thus, the decrease in rate, over a shorter range, of the series of alkyl methylphosphonate adducts (60; R = alkoxy, R' = Me) could then principally arise from the effects of steric hindrance of the ester moiety only.

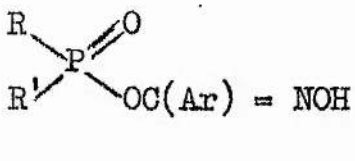
This proposal is strengthened by the diminution in the rate of acid hydrolysis of the adducts (60; R = alkoxy) caused by increasing alkyl substitution at the phosphorus atom (Table 32). The ratio of $k_{Me}/k_{Bu}t$ = 180 is more nearly that observed for the

alkaline hydrolysis of diisopropyl alkylphosphonates[61] of $k_{Me}/k_{Bu^t} = 500$. In this case the phosphorus atom in the adducts (60) receives in full the steric and electronic effects associated with the alkyl groups, because protonation of the ester moiety can have little influence on effects transmitted directly to phosphorus.

The diethyl phosphate adduct (60; R = R' = OEt) and the ethyl t-butylphosphonate adduct (60; R = OEt, R' = Bu^t) are two cases where the normal acid hydrolysis is complicated by the much greater rate of the alkaline hydrolysis. The ethyl t-butylphosphonate adduct (60; R = OEt, R' = Bu^t) hydrolysed by both routes at pH 2·50 to give both ethanol and p-nitroaniline. In spite of there being only a low concentration of the anion, the rate of alkaline hydrolysis is sufficient to produce a measurable quantity of p-nitroaniline. The rate coefficient-pH profile increased with increasing pH for the diethyl phosphate adduct (60; R = R' = OEt) at 25° due to the very rapid reaction in the alkaline region (half-life at pH 8·50, 0·75 minutes).

The acid hydrolysis of the diethyl phosphate adduct is similar to that of diethyl o-carboxyphenylphosphonate, in that the second ester moiety is lost at a much slower rate than the first. However, Blackburn and Brown[90] have demonstrated that nucleophilic catalysis by the carboxyl group occurs in the o-carboxylic ester

rather than direct bimolecular substitution by water.



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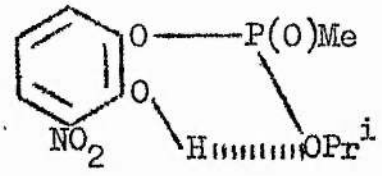


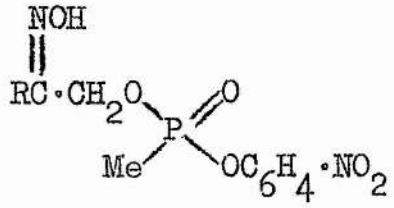
(65)

A number of acid-catalysed hydrolyses of phosphorus esters were discussed in the Introduction. The hydrolysis of isopropyl 3-nitro-2-hydroxyphenyl methylphosphonate (65) is of greatest relevance to the present work. Mlodozeniec[88] found a similar pH-rate profile in the range pH 2-7, but the fall-off in rate began at pH 4·5, in accordance with the pK_a of the phenol being slightly greater (pK_a 5·55) than that of the alkyl alkylphosphonate adducts (60; R = alkoxyl) with pK_a about 4·6. The unimolecular rate constant for loss of isopropanol was slower ($\times 10^{-1}$) than the oxime-assisted reaction. He proposed that the loss of the isopropyl moiety was internally acid catalysed and promoted with nucleophilic attack of water on the neutral ester species.

Mlodozeniec also reported the energy and entropy of activation as 13·9 Kcals./mole and -30 eu, respectively. These correspond well to the values obtained by Maynard[139] for the acid hydrolysis of the ethyl methylphosphonate adduct (60; R = OEt, R' = Me) of 14·9 Kcals./mole and -19 eu.

The hydrolysis of p-nitrophenyl phenacyl methylphosphonate

oxime (28) was shown[95] to hydrolyse via an oximate anion-catalysed water-mediated reaction. It thus reacts by an entirely different mechanism from the adducts described in the present work.



(28)

Hydrolysis in Alkaline Solution, pH 8-9

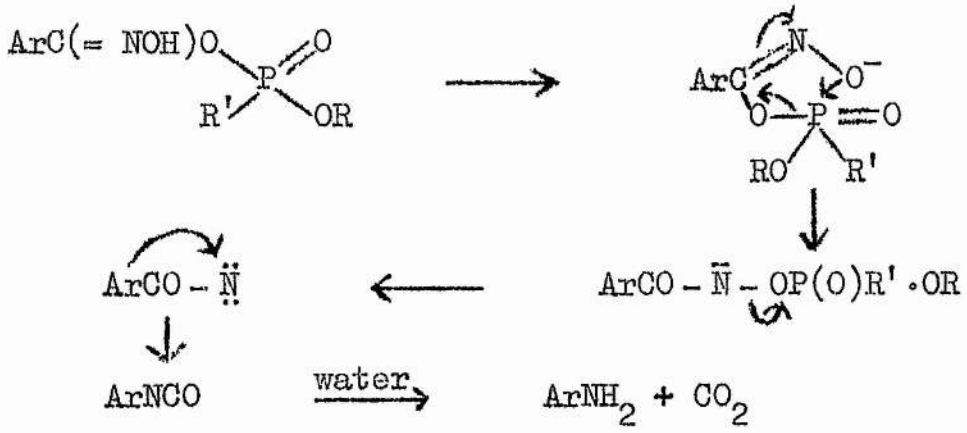
The rates of reaction (Table 25, page 162) for the alkyl alkylphosphonate adducts (60; R = alkoxy) are almost constant over the pH range 8-9, falling only very slightly at pH 9. The rates are also very similar to one another, there being only a factor of 2·5 between the fastest and the slowest (Figures 1 and 2, pages 182 and 183).

At pH 8-9, the form of the kinetics followed a rapid deprotonation of the oxime moiety with a slower first-order decomposition to yield the phosphorus acid anion and p-nitroaniline.

p-Nitrophenyl cyclohexyl urea was obtained from the decomposition of the propyl methylphosphonate adduct (60; R = OPr, R' = Me) in cyclohexylamine; and this, together with the quantative formation of p-nitroaniline in the hydrolyses, indicates the

intermediacy of p-nitrophenyl isocyanate. No pinacolyl alcohol was detected in the hydrolysis of the pinacolyl methylphosphonate adduct (60; R = OCHMe·Bu^t, R' = Me). There was no reaction to form p-nitroaniline in the methylated oxime adduct derived from the neopentyl methylphosphonate adduct (60; R = OCH_2.Bu^t, R' = Me), where no oximate anion could be formed.

p-Nitrophenyl isocyanate is considered to arise by initial attack of the oxime anion, formed by deprotonation, on the phosphorus atom to yield a five-membered ring intermediate (Scheme 12).



Scheme 12

After rupture of the phosphorus-benzyloxygen bond, there remains a phosphonylated benzhydroxamate which rapidly loses the phosphorus acid anion (phosphorus acid anions are good leaving groups) to create an electron-deficient nitrogen atom. This deficiency is then satisfied by migration of the p-nitrophenyl group to yield the isocyanate via a Lossen rearrangement. Under the conditions of

the hydrolysis, attack of water on the isocyanate to yield p-nitroaniline is instantaneous. Such a mechanism is consistent with the observed first-order kinetics.

The intramolecular attack of oximate anion has previously been postulated by Alexandrou and Nicolaides[169] to account for the formation of aryl benzamides from the adducts of benzonitrile oxide and the sodium salts of carboxylic acids (page 175). Similar breakdown of phosphonylated oximes and hydroxamic acids (to give isocyanates) was traced in the Introduction. In particular, Samuel and Silver[78] confirmed that the attack of a hydroxamic acid on diisopropyl phosphorofluoridate was rate-determining. The phosphorylated hydroxamate subsequently spontaneously decomposed to yield the acid anion rather than by nucleophilic displacement with water.

Westheimer[98] has rationalised the unique, rapid hydrolysis of five-membered cyclic phosphorus esters in terms of the pseudo-rotation of pentacovalent intermediates. Subsequently to Westheimer's review,[98] a number of workers (page 111) reported mechanisms involving the intra-molecular formation of five-coordinate intermediates, which then underwent pseudo-rotation, to account for the rate of reaction[133] and the products observed.[131,132]

The alkaline hydrolyses of the alkyl α-hydroxyimino-p-

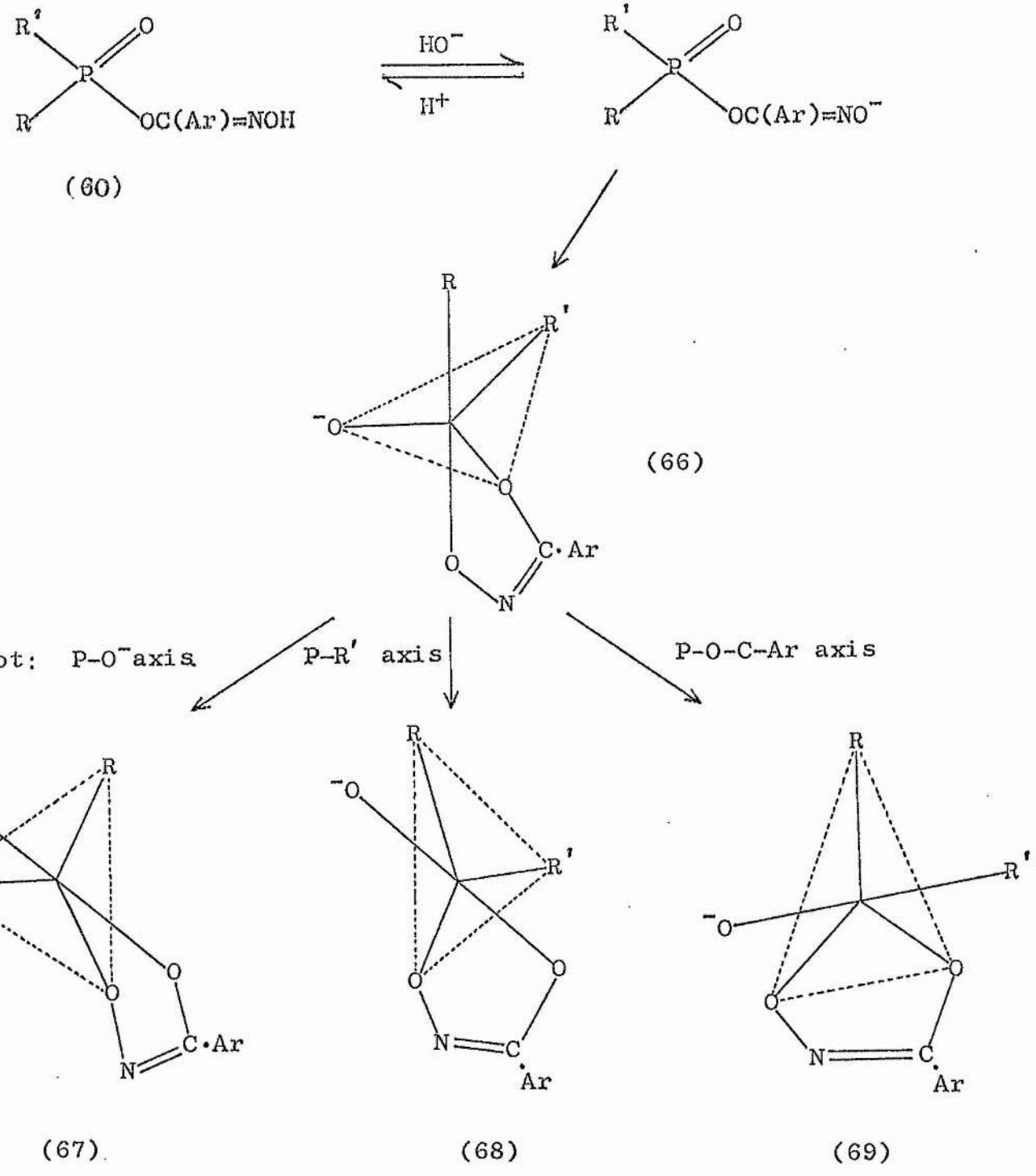
-nitrobenzyl alkylphosphyls (60) is also postulated to proceed via a five-coordinate intermediate to account for both the rate of reaction and the difference in the rates of reaction between the diethyl phosphate adduct (60; R = R' = OEt) and the diethylphosphinate adduct (60; R = R' = Et).

The conditions and constraints for pseudo-rotation were discussed in the Introduction. In the present work, initial rapid deprotonation of the oxime moiety is assumed to be followed by apical attack on phosphorus to form a pentacoordinate intermediate (Scheme 13).

The initially-formed pentacovalent intermediate (66) is formed with an alkoxyl group in the apical position and an alkyl group in an equatorial position, in accordance with the stated preference rules.[118] It is necessary for the initial form to undergo pseudo-rotation, so as to allow the benzyl-oxygen bond to break from the (preferred) apical position.

The pseudo-rotated form (69) is expected to be energetically unfavourable, since it requires the ring angle at phosphorus to be expanded to 120°. The forms (67) and (68) possess the five-membered ring lying in the energetically favourable apical-equatorial position and the leaving group in the required apical position. However, (68) is rejected on the basis of Frank and Usher's[132]

Scheme 13. Formation of Penta- coordinate Intermediates in the Alkaline Rearrangement of Alkyl α-hydroxyimino-p-nitrobenzyl alkylphosphyls.



(60) (66) (67) (68) (69)

requirement that the phosphoryl group remain in an equatorial position in the pseudo-rotated forms, for the two available pathways of the reaction of dimethyl phosphoroacetoin and its related methyl methylphosphonoacetoin. Boyd[118] has confirmed by molecular orbital calculations on 2-oxo-2-methoxy-1,3,2-dioxaphospholan the general higher energies of pentacovalent structures with apically directed phosphoryl bonds.

Thus, the pseudo-rotated form (67) is the one that is most likely to be formed if the preference rules are obeyed.[118] The pentacoordinate intermediate (67) will be more readily formed from the diethyl phosphate adduct (60; R = R' = OEt) than from either the ethyl ethylphosphonate adduct (60; R = OEt, R' = Et) or the diethylphosphinate adduct (60; R = R' = Et), because the apical group R' is alkoxyl rather than alkyl. It has been shown[132] that the formation of the pentacoordinate intermediate in which one of the apical groups is alkyl, is inhibited (see page 114).

The rates of formation of p-nitroaniline parallel the ease of formation of the pseudo-rotated form (67), which is greatest for the diethyl phosphate adduct (60; R = R' = OEt). The relative rates are summarised:

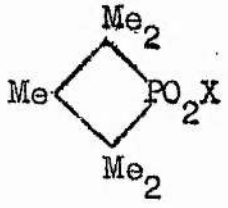
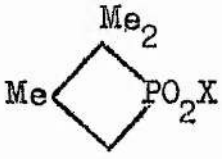
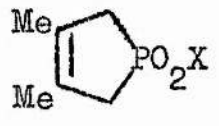
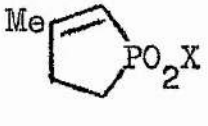
Adduct	Rel. Rate
Diethyl phosphate (60; R = R' = OEt)	140
Ethyl ethylphosphonate (60; R = OEt, R = Et)	10
Diethylphosphinate (60; R = R' = Et)	1

The formation of the initial pentacoordinate intermediate (66; R = R' = Et) is inhibited for the diethylphosphinate adduct (60; R = R' = Et) because of the apical ethyl group, whereas for the other two adducts the initial apical group is (preferred) ethoxyl.

The rates of reaction of the cyclophosphinate adducts are more rapid (Table 33) than the acyclic diethylphosphinate adduct (60; R = R' = Et) due to the relief of strain in forming the initial trigonal bipyramid (66). The rates of rearrangement for the cyclic five-membered adducts (Table 33) are intermediate between

Table 33

Rates of Alkaline Hydrolysis of the Cyclic Phosphinate Adducts (60) relative to α-Hydroxyimino-p-nitrobenzyl diethylphosphinate

Adducts*				
Rel. Rate	8·5	6·1	2·2	4·5

* X = -C(Ar) = NOH

that of the acyclic diethylphosphinate adduct (60; R = R' = Et) and the cyclic four-membered ring adducts (Table 33). This

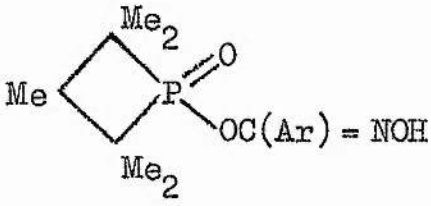
probably reflects the reduced strain inherent in a five-membered ring when compared with a four-membered ring.

The order of reactivity observed for the cyclo-phosphinate adducts (Table 33) parallels the behaviour of the simple cyclic phosphinate esters (page 110). Five-membered cyclic phosphinate esters show a slight acceleration of hydrolysis in alkaline solution, but strained five-membered rings (at a bridge-head) or four-membered rings are still more reactive.

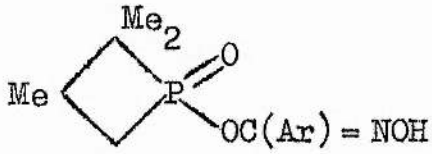
It is noteworthy how similar the rates of alkaline hydrolysis of the alkyl alkylphosphonate adducts (60; R = alkoxy) are to one another (Figures 1 and 2, pages 182 and 183 respectively). In particular, steric factors appear to have little influence on the reaction rate. The ethyl t-butylphosphonate adduct (60; R = OEt, R' = Bu^t) hydrolyses at almost the same rate as the ethyl methylphosphonate adduct (60; R = OEt, R' = Me). This is to be compared with the acid hydrolysis of the two adducts, in which the former reacts more slowly (x 10^{-2}) than the latter. This is similar to the behaviour observed in the alkaline hydrolysis of the simple diisopropyl methyl- and diisopropyl t-butyl-, phosphonates where strong steric hindrance causes a large rate decrease.[61]

The lack of a steric hindrance in the alkaline hydrolysis (Table 33) of the adducts (60) is again clearly shown in the two

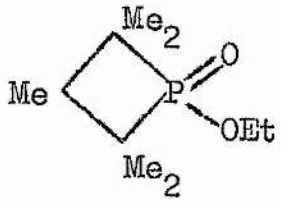
four-membered ring phosphinate adducts (70) and (71). Trippett[130] observed a rate difference between the two cyclic esters (43) and (44) of about 4×10^3 and explained the slower rate of hydrolysis of the more highly substituted ester (43) by its increased steric



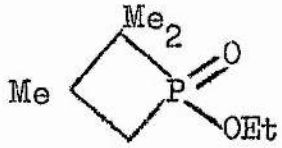
(70)



(71)



(43)



(44)

hindrance to the attacking nucleophile. However, there is little difference between the rates of the two four-membered cyclic phosphinate adducts, (70) and (71) (Table 33); and in fact the more highly substituted ring phosphinate adduct (70) is the more reactive, contrary to the observed reactivity of (43) and (44).

To investigate further the reactivity in the alkaline rearrangement, activation parameters (Table 28, page 168) were determined for a number of the adducts (60).

The values of the activation energies are generally quite

similar to one another. However, they are higher than those values normally associated with nucleophilic attack at phosphorus. Cox and Ramsay[171] list in their reveiw activation energies for the alkaline hydrolyses of phosphates, phosphonates, and phosphyl chlorides, in different solvents. Their values lie in the range 8-16 Kcals./mole.

There appears to be a trend such that the activation energy is greatest for substituents which are capable of increasing the electronic charge at phosphorus, either inductively (60; R = OEt, R' = Bu^t) or mesomerically (60; R = R' = OEt). The activation energy also increases with increasing alkyl substitution in the ester moiety. Similar trends have been reported in the literature for the hydrolyses of other phosphorus compounds (pages 70-73). This lends support to the proposed attack of the oximate anion on the phosphorus centre in the initial formation of the cyclic intermediate.

It is interesting to speculate on why the value of the activation energy should be as high as 19-22 Kcals./mole. It is tempting to ascribe this to the formation of the pentacoordinate intermediate where the stability of the phosphoryl group is lost.

The value of the entropy of activation is a measure of the order of the transition state of the substrate and the surrounding

solvating medium. It is difficult to account for small entropy effects, although there are a few generalisations that may be made.[172] Reactions in which the total number of molecules decreases are usually attended by a negative entropy of activation. Similarly, if a cyclic transition state is formed from non-cyclic products, a negative entropy of activation is to be expected since free rotation about the bonds becomes restricted during the cyclisation. A low entropy of activation may also reflect a crowded transition state in which freedom of motion of the substituents is unduly hindered. Conversely, a unimolecular dissociation reaction is likely to have a positive entropy of activation, since there is greater randomness of the product system.

The values of the activation entropies (Table 28, page 168) show that there is an increase in the order of the transition state which can be associated with the proposed cyclic transition state (Scheme 13, page 199). The oximate moiety would be expected not to show a great loss in its degrees of freedom in forming the transition state, since the configuration of the C = N bond holds the anion in a position that is favourable for attack in a five-membered transition state leading to the intermediate.

Some relief of steric strain is to be expected in the formation of the penta-covalent intermediate because the local geometry

at the phosphorus atom is relaxed from its tetrahedral configuration. It is known that the apical bonds lengthen significantly and some relief of strain may be possible. This should be most marked in the ethyl t-butylphosphonate adduct (60; R = OEt, R' = Bu^t), where the bulky t-butyl group is able to move away from the phosphorus atom and reduce the interaction. Support for this proposal comes from the higher $\Delta S^{\ddagger}$ value of + 0.5 eu compared with the ethyl ethylphosphonate adduct (60; R = OEt, R' = Et), where the value is - 11.4 eu.

The $\Delta S^{\ddagger}$ values for the two cyclic four-membered phosphinic acid adducts (70) and (71) are lower than that of the diethylphosphinate adduct (60; R = R' = Et) and this may again be due to the relief of strain as the apical bond lengthens (Table 28, page 168). Although there is only a small difference between the activation entropies for the two adducts, the lower value for the more highly substituted adduct (70) could reflect the steric interaction between the methyl groups attached to the carbon atom lying in the equatorial plane and the remainder of the pentacoordinate intermediate.

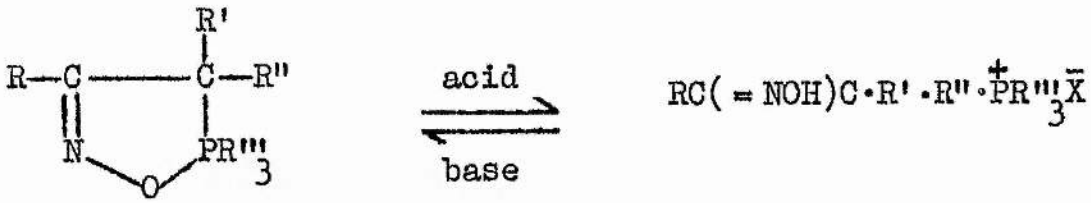
It is difficult to account for the high positive value of the entropy of activation for the diethyl phosphate adduct (60; R = R' = OEt). A contributory factor to the value of $\Delta S^{\ddagger}$ compared with

the alkyl alkylphosphonate adducts (60; R = alkoxy) is that in the diethyl phosphate adduct (60; R = R' = OEt) there are two ethoxy groups at which the initial backside attack may occur, whereas for the alkyl alkylphosphonate adducts there is only one ethoxyl group. Thus, there are more restrictions on the intramolecular attack in the alkyl alkylphosphonate adducts, which is reflected in a lower value of $\Delta S^{\ddagger}$.

Up to now the role of the solvating medium has been neglected. In the Introduction it was noted that the entropy of activation generally decreased for phosphorus esters in the order of phosphinates, phosphonates, and phosphates. The decrease has been ascribed to the reduced need of solvation by alkoxyl substituted compounds.[65] The negative charge is partially stabilised in the transition state by the oxygen atoms of the alkoxyl substituents. A similar effect could account for the higher reactivity of the alkyl alkylphosphonate adducts (60; R = alkoxy) compared with the dialkylphosphinate adducts (60) and also for the still greater reactivity of the diethyl phosphate adduct (60; R = R' = OEt). This proposal is supported by the values of $\Delta S^{\ddagger}$ (Table 28, page 168), which decrease generally in the order dialkylphosphinate adducts (60), alkyl alkylphosphonate adducts (60; R = alkoxy) and diethyl phosphate adduct (60; R = R' = OEt).

The greater reactivity (Table 25, page 162) of the ethyl phenylphosphonate adduct (60; R = OEt, R' = Ph) when compared with the methyl methylphosphonate adduct (60; R = OMe, R' = Me) is unexpected. The phenyl group has a π charge cloud associated with it and is thus more electronegative than an alkyl group. It might then be expected to possess some of the characteristics of an alkoxyl group for the purposes of pseudo-rotation. Thus, the formation of the pseudo-rotated form (67) should be less inhibited than the corresponding alkyl alkylphosphonate adduct (60; R = alkoxy), with a consequent increase in the rate of reaction to between that of the diethyl phosphate adduct (60; R = R' = OEt) and the remainder of the alkyl alkylphosphonate adducts (60; R = alkoxy).

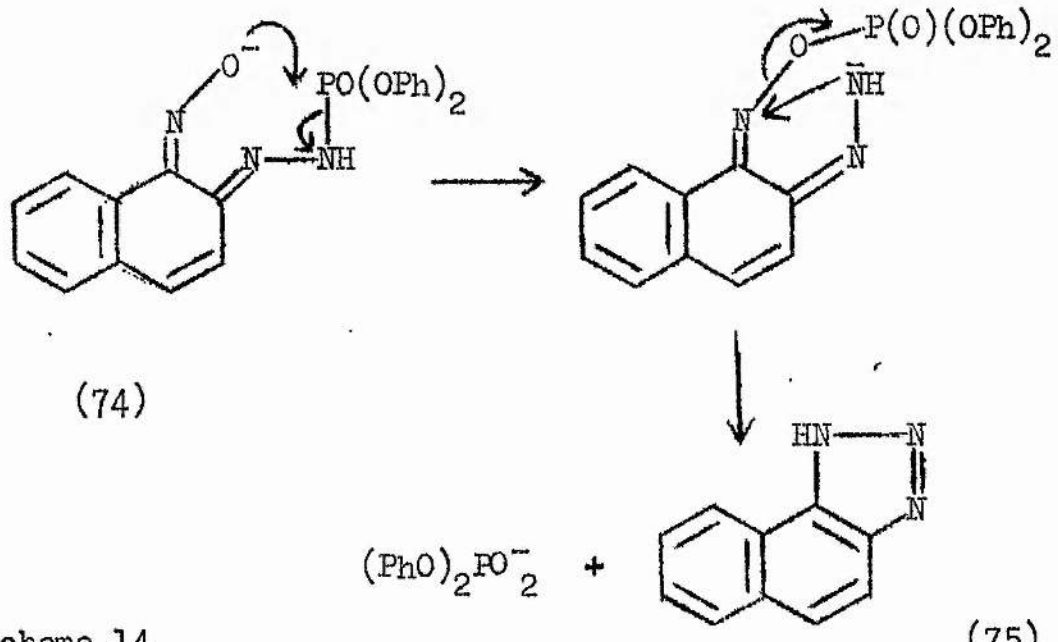
Gaudiano[173] et al. have recently reported the formation of 1,2,5-oxazaphosph(V)ol-2-ines (72) from 2-oximino-phosphonium salts (73). The compounds (72) were obtained in high yield by percolating an ethanolic solution of the phosphonium salt (73) through a basic ion exchange resin. The ease of formation of the ring compound (72) in this case suggests that the deprotonated oximate anion is well positioned in the molecule to easily complete the five-membered ring. By analogy, the deprotonated oximate anion is equally well positioned for the formation of the initial pentacoordinate intermediate (66: Scheme 13, page 199) in the adducts (60)



(72) (73)

described in the present work.

Lalor and Scott[174] have recently described the conversion of 1,2-naphthaquinone-1-oxime-2-(O,O'-diphenyl)-phosphorohydrazone (74) in boiling dilute aqueous potassium carbonate solution to 1H-naphtho[2,1-d][1,2,3]triazole (75) in 89% yield (Scheme 14). This involves initial attack by the oximate anion at phosphorus with the subsequent rupture of the phosphorus-hydrazone bond. On the basis of the presently available evidence it is impossible to decide whether this initial step proceeds synchronously or via a



(74) (75)

Scheme 14

five-coordinate intermediate. However, both the work of Gaudiano[173] and that of the present thesis lend support to this reaction scheme suggested by Lalor and Scott.[174]

Conclusions

The lability of the proton of the oxime moiety in the addition products of p-nitrobenzonitrile oxide and phosphorus acids, $RR'P(O)OC(p\text{-}NO_2C_6H_4)=NOH$, renders the adducts not particularly suitable as a means of reactivating "aged" acetyl cholinesterase. The route of hydrolysis changes smoothly after pH 3, due to increasing deprotonation of the oxime, to an intramolecular process whereby p-nitroaniline is formed rather than displacement of the ester moiety. The blood pH of the human body is 7·4 and at this pH most of the adduct exists as the anion, so that exclusive p-nitroaniline formation occurs. If the adducts were to be of use in the reactivation of "aged" acetyl cholinesterase, then hydrolysis of the ester moiety would be required at pH 7·4.

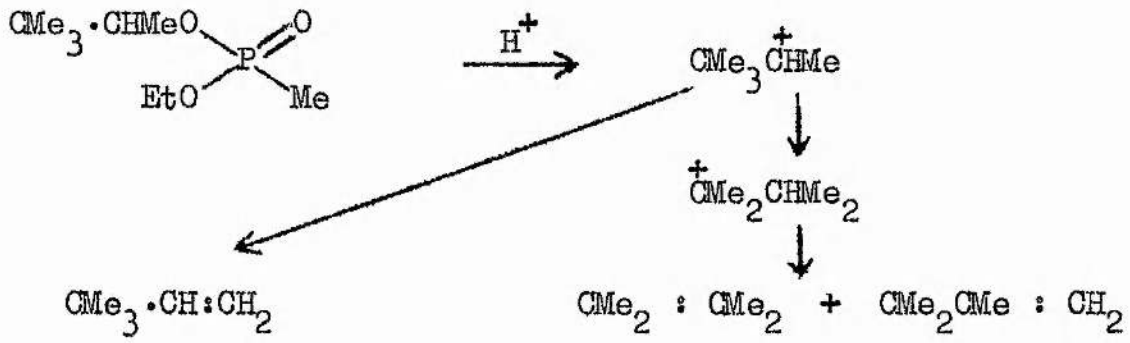
Nevertheless, the adducts exhibit extremely rapid, intramolecularly catalysed acid hydrolysis by water at the phosphorus atom. Even the pinacolyl ester moiety, $Bu^t\cdot CHMeO-$, which is known for its ease of carbonium ion formation, is displaced as the alcohol in acid solution. One result from the study of the effects of

different ester moieties at phosphorus is the compression of the reactivity range normally associated with these substituents. It is suggested that this effect results almost entirely from the steric influences of the ester moieties.

Cyclic pentacoordinate intermediates are postulated to be formed in the alkaline hydrolysis to yield p-nitroaniline. The results obtained in the present work contribute to the growing body of experimental evidence which supports the formation of such intermediates in the reactions of phosphorus compounds.

The Hydrolysis of Ethyl Pinacolyl Methylphosphonate

The acid hydrolysis of the ester proceeds with carbon-oxygen fission to yield hydrogen ethyl methylphosphonate and three olefins. It is considered that the formation of the rearranged olefins, 2,3-dimethylbut-1-ene and 2,3-dimethylbut-2-ene indicates the intermediacy of the pinacolyl carbonium ion, thus:



Skell and Reichenbacher[175] have confirmed that these olefins do arise from the pinacolyl cation and its rearranged cation by anodic oxidation of pinacolyl carboxylate. They found that the extent of rearrangement was greater below pH 14, the rate of methyl migration being 10^{-10} $sec.^{-1}$

The higher rate of production of these olefins from the ester when compared with that from pinacolyl alcohol itself (about 25:1), together with the absence of pinacolyl alcohol among the products of an interrupted hydrolysis, is evidence for the pinacolyl carbonium ion being yielded by direct carbon-oxygen fission of the

ester rather than via the intermediacy of pinacolyl alcohol formed by phosphorus-oxygen fission.

Within the experimental error, the rates of production of the olefins and the acid product are equal. Although the rate constant determined by acidimetry is $3\frac{1}{2}$ times that determined by olefin titration, the same method also shows that the rate of dehydration of the alcohol is slower than ester hydrolysis by at least a factor of 8. The limiting factor in the accuracy of the results was the volatility of the olefins.

It can now be regarded that the work of Cadogan,[135] Keay,[83] and Hudson and Keay[61] is unequivocal proof that acyclic secondary alkyl phosphonate esters undergo acidic hydrolysis with carbon-oxygen fission.

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